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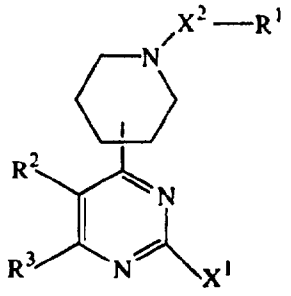
(54) Title: PIPERIDINYLPYRAMIDINE DERIVATIVES

(57) Abstract

A compound of formula (1) wherein; X^1 is amino or hydroxyl, X^2 is carbonyl and the like, R^1 is an alkyl, an aryl and the like, R^2 is hydrogen and the like, and R^3 is an alkyl and the like, or a pharmaceutical acceptable salt thereof, is effective for inhibiting the production and/or secretion of tumor necrosis factor in a patient in need of such inhibition.



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DESCRIPTION

PIPERIDINYLPYRIMIDINE DERIVATIVES

Technical Field

The present invention relates to a method for inhibiting the production and/or secretion of tumor necrosis factor, a pharmaceutical composition inhibiting the production and/or secretion of tumor necrosis factor and novel piperidinylpyrimidine derivatives.

Background Art

Tumor necrosis factor alpha (hereinafter abbreviated as TNFα) is a peptide of 157 amino acids, having a molecular weight of about 17,000. TNFα is a cytokine produced from various cells including activated macrophages.

Although TNFα is a cytokine showing cytotoxicity against several kinds of tumor cells, subsequent studies revealed that TNFα has various other activities, and the activities are not only limited to tumor cells but extend to many other normal cells. The diverse effects of TNFα are markedly enormous. Examples of the TNFα activities are suppression of lipoprotein lipase activity in adipocytes; expression of human leukocyte antigens (HLA) on blood endothelial cells and fibroblasts; interleukin-1 production by fibroblasts or

macrophages; activation of macrophages; induction of colony stimulating factor by fibroblasts, endothelial cells or some tumor cells; inhibition of synthesis of proteoglycans and stimulation of their resorption in cartilage; activation of neutrophils and generation of superoxide; production of procoagulant factor by blood endothelial cells; proliferation of fibroblasts; IL-6 production by fibroblasts; injury of blood endothelial cells; and the like. According to recent studies, TNFα is recognized as a cytokine involved broadly in vital protection through inflammation and immune response, as described in Vassalli, P., Ann. Rev. Immunol., 10, 411-452 (1992).

On the other hand, it has been found that continuous or excessive production of TNFα can result in extreme action on normal cells which can cause various diseases. It is also reported in Beutler B., Greenwald D., Hulmes J.D. et al., Nature, 316, 552-554 (1985), Kawakami, M., SEIKAGAKU (Biochemistry), 59, 1244-1247 (1987) that TNFa is also known as cachectin, which induces cachexia in cancer or infectious diseases (involving catabolic acceleration of total metabolism leading to extreme wasting).

TNFα is considered to be one of the causes of septic shock and there are many reports on the effectiveness of an anti-TNFα antibody in septic shock (Starnes, H.F. Jr., Pearce, M.K., Tewari, A., Yim, J.H., Zou, J.C., Abrams, J.S., J. Immunol., 145, 4185-4191

(1990), Beutler, B., Milsark, I.W., Cerami, A.C., Science, 229, 869-871 (1985), Hinshaw, L.B., Tekamp-Olson, P., Chang, A.C.K. et al., Circ. Shock, 30, 279-292 (1990)).

An increased level of TNFα is also found in the synovial fluid or blood from rheumatoid arthritis patients, as reported in Tetta, C., Camussi, G., Modena, V., Vittorio, C.D., Baglioni, C., Ann. Rheum. Dis., 49, 665-667 (1990).

In recent years, acquired immunodeficiency syndrome (AIDS) has been explosively prevalent all over the world. AIDS is a disease mainly caused by infection with human immunodeficiency virus-1 (HIV). HIV-infected patients are often complicated by opportunistic infections, Kaposi's sarcoma, neurological disorders (CNS disorders), and/or cachexia, etc., and those deseases often cause fatal.

HIV is a retrovirus classified in the subfamily of Lentiviruses. CD4-positive T lymphocytes and monocytes are the major cellular targets for HIV infection, but HIV also infects other various cells such as macrophages, glial cells and the like. HIV is integrated into the host cell chromosomes as a provirus DNA by means of viral enzymes such as reverse transcriptase and integrase. A new viral RNA is transcripted by the provirus. The viral RNA comprises regions encoding proteins constituting HIV and is translated into the proteins to produce new virions together with the viral RNA. The transcription of

retoroviral RNA is mainly controlled by the virus-specific nucleotide sequence named a long terminal repeat (LTR) which is a sequence repeated upstream of the 5' end of integrated retroviral proviruses. The LTR region contains control sites for initiation and elongation of transcription, i.e., binding sites for a plurality of transcription factors in a host cell and transcription activators derived from viruses. Accordingly, it is considered that the transcription of HIV genes would be controlled depending upon the amount of these factors/activators present in the cells (Green, W.C., Annu. Rev. Immunol., 8, 453-475 (1990)).

It is known that in T cells or macrophages stimulated by, e.g., antigens, a lipopolysaccharide, which is one of the main constituents of bacteria, proinflammatory cytokines (TNFα, IL-1 or IL-6) or PMA, signal transduction pathways in cells are activated and unique sets of activated transcription factors increase in the nucleus to accelerate the transcription of HIV (Osborn, L. et al., Proc. Natl. Acad. Sci., USA, 86, 2336-2340 (1989), Poli, G. et al., J. Exp. Med., 172, 151-158 (1990), Poli, G. et al., Proc. Natl. Acad. Sci., USA, 87, 782-785 (1990)).

It is interesting to note that some of the binding sites of those transcription factors contained in the LTR sequence are also found in the enhancer/promoter region of viral genes, such as Rous sarcoma virus, human cytomegalovirus and simian virus, and in the

enhancer/promoter region of various vital genes including TNFα (Shakhov, A.N., J. Exp. Med., 171, 35-47 (1990)). It is known that the corresponding transcription factors take some role in activation of the transcription of these genes. It is then suggested that some inhibitors of TNFα production may reduce not only the transcription of TNFα but HIV by interfering directly/indirectly with the activity of these transcriptional factors (Li, C.J. et al., Trends in Microbiology, 2(5), 164-169 (1994)).

On the other hand, an abnormally high concentration of TNFα in blood of AIDS patients is reported (Dezube, B.J. et al., J. Acquir, Immune Defic. Syndr. 5, 1099-1104 (1992), Wright, S.C. et al., J. Immunol, 141(1), 99-104 (1988)). The excessive production of TNFα in the AIDS patients is another evidence suggesting that TNFα would be associated with pathological conditions including cachexia, apoptosis of T cells, abnormal B cells proliferation, etc., in addition to the activity of accelerating HIV proliferation. By reducing the level (concentration) of TNFα in a host, an inhibitor of TNFα or an inhibitor of production and/or secretion of TNFα is therefore expected to show not only the activity of inhibiting HIV proliferation but the activity of improving the pathological conditions of AIDS described above.

In addition, there are many other diseases wherein a high concentration of TNFα is found in blood and/or tissue, e.g., osteoarthritis (Venn, G., Nietfeld,

J.J., Duits, A.J., Brennan, F.M., Arner, E., Covington, M., Billingham, M.E.J., Hardingham, T.E., Arthritis Rheum., 36(6), 819-826 (1993)); multiple sclerosis (Sharief, M.K., Hentges, R., N. Engl. J. Med., 325 (7), 467-472 (1991)); Kawasaki disease (Matsubara, T., Furukawa, S., Yabuta, K., Clin. Immunol. Immunopathol., 56, 29-36 (1990)); inflammatory bowel diseases such as ulcerative colitis or Crohn's disease (Murch, S., Walker-Smith, J.A., Arch. Dis. Child, 66, 561 (1991); Maeda, Y., SHOKAKI-TO-MEN-EKI (Digestive Organ and Immunity), 22, 111-114 (1989)); Behçet disease (Akoglu, T., Direskeneli, H., Yazici, H., Lawrence, R., J. Rheumatol., 17, 1107-1108 (1990)); systemic lupus erythematosus (SLE) (Maury, C.P.J., Teppo, A-M., Arthritis Rheum., 32, 146-150 (1989)); graft versus host disease (GvHD) (Nestel, F.P., Price, K.S., Seemayer, T.A., Lapp, W.S., J. Exp. Med., 175, 405-413 (1992)); multiple organ failure (Fujiwara, T., Kawakami, M., RINSHO-I (Clinician), 17 (10), 2006-2008 (1991)); malaria (Grau, G.E., Fajardo, L.F., Piguet, P.F., et al., Science, 237, 1210-1212 (1987)); meningitis (Waage, A., Halstensen, A., Espevik, T., Lancet, I, 355-357 (1987)); hepatitis (Sugano, K., KANZO (Liver), 33, 213-218 (1992)); non-insulin-dependent diabetes mellitus (NIDDM) (Hotamisligil, G.S., Shargill, N.S., Spiegelman, B.M., Science, 259, 87-91 (1993), asthma, adult respiratory distress syndrome (ARDS), tuberculosis, atherosclerosis, Alzheimer's disease, etc.

As seen from the above publications, it is

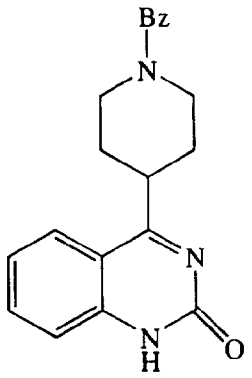
understood that excessive production of TNFα sometimes adversely affects the living body. Therefore, further investigation is desired to develop an inhibitor of production and/or secretion of TNFα or TNFα inhibitors available for the treatment of these diseases.

As compounds and factors showing an activity of inhibiting TNFα, pentoxifylline, glucocorticoid, protease inhibitors, phospholipase A2 inhibitors, lipoxygenase inhibitors, platelet activating factor (PAF) antagonists, radical scavengers, prostaglandin F_2 or I_2, an anti-TNFα antibody, thalidomide, etc. are known. However, these compounds or factors are accompanied by side effects because of a diversity of their pharmacological activities. It is therefore required to develop highly safe compounds based on a novel mechanism.

TNFβ (lymphotoxin, LT) is also known as a factor belonging to the same family of TNFα. TNFβ is a glycoprotein composed of 171 amino acids, and has homology with TNFα both in gene structure and amino acid sequence. Further, it is known that both TNFβ and TNFα commonly share the same receptors and have identical biological activities. The enhancer/promoter regions at the upstream of TNFα and TNFβ genes have a common partial sequence to which the same transcriptional factors possibly bind. TNFβ may be produced by stimulation with antigen, phorbol ester and mitogen which are known to induce the production of TNFα. Thus, factors or compounds having an inhibitory activity on the production

of TNFα may also exhibit an inhibitory activity on TNFβ (Jongeneel, C.V., Tumor Necrosis Factors; Beutler, B. Ed., Raven Press: New York, 1992, pp. 539-559, Poter, A.G., FEMS Microbiol. Immunol., 64, 193-200 (1990), Pauli, U., Critical Rev. Eukaryotic Gene Expression, 4, 323-344 (1994)).

On the other hand, piperidinylpyrimidine derivatives are described in WO 9426733 and Japanese Patent KOKOKU No. 49-11710. However, these publications do not suggest any TNFα inhibitory activities. In Chem. Pharm. Bull., 34 (5), 1907-1916 (1986) the description, which is limited to use as intermediates for synthesis, discloses compounds represented by the following formula:



(wherein Bz is benzoyl.).

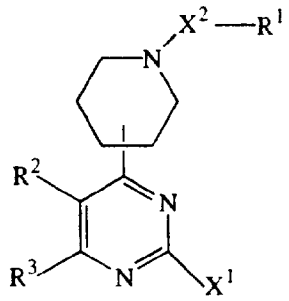
No utility of these compounds is disclosed anywhere in the report.

Disclosure of Invention

This invention provides a method for inhibiting the production and/or secretion of tumor necrosis factor, a pharmaceutical composition inhibiting the production

and/or secretion of tumor necrosis factor and novel piperidinylpyrimidine derivatives having an excellent activity of inhibiting the formation and/or secretion of TNFα.

The present invention relates to a method for inhibiting the production and/or secretion of tumor necrosis factor in a patient in need of such inhibition, which comprises administering to a patient a pharmaceutically effective amount of a compound represented by formula (1)



(1)

wherein X^1 is amino or hydroxy;
X^2 is carbonyl (-(CO)-), carbonyloxy (-(CO)O-), carbonylamino (-(CO)NH-), or sulfonyl (-(SO_2)-);
R^1 is an alkyl, a cycloalkyl, an aryl, a substituted aryl, a heteroaryl, or -$(CH_2)_m$- A, wherein m is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and A is a halogen atom, a cycloalkyl, hydroxy, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a

saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

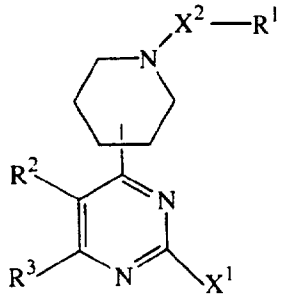
R^2 is hydrogen, an alkyl, or an aryl;

R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-$ A', wherein m' is an integer selected from the group consisting of 1, 2, 3, and 4, and A' is a halogen atom, a cycloalkyl, hydroxy, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

or R^2 and R^3 are combined together with the pyrimidine ring to form quinazoline, a substituted quinazoline, pyridopyrimidine or a substituted pyridopyrimidine;

or a pharmaceutically acceptable salt thereof.

This invention also relates to a pharmaceutical composition comprising a compound represented by the formula(1);



(1)

wherein X^1 is amino or hydroxy;

X^2 is carbonyl (-(CO)-), carbonyloxy (-(CO)O-),

carbonylamino (-(CO)NH-), or sulfonyl (-(SO_2)-);

R^1 is an alkyl, a cycloalkyl, an aryl, a substituted aryl, a heteroaryl, or -$(CH_2)_m$- A, wherein m is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and A is a halogen atom, a cycloalkyl, hydroxy, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

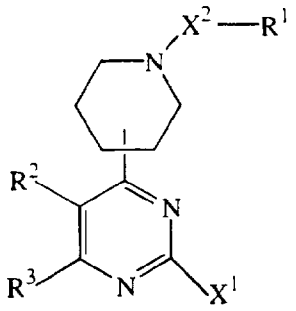
R^2 is hydrogen, an alkyl, or an aryl;

R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or -$(CH_2)_{m'}$- A', wherein m' is an integer selected from the group consisting of 1, 2, 3, and 4, and A' is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

or R^2 and R^3 are combined with the pyrimidine ring to form quinazoline, a substituted quinazoline, pyridopyrimidine or a substituted pyridopyrimidine;

or a pharmaceutically acceptable salt thereof.

This invention also relates to a piperidinylpyrimidine derivative represented by the formula (1-a)



(1-a)

wherein

(1) X^1 is amino or hydroxy;

X^2 is carbonyl (-(CO)-), carbonyloxy (-(CO)O-), carbonylamino (-(CO)NH-), or sulfonyl ($-(SO_2)-$);

R^1 is an alkyl, a cycloalkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_m-$ A, wherein m is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, and A is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkokycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

R^2 is hydrogen, an alkyl, or an aryl;

R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-$ A', wherein m is an integer selected from the group consisting of 1, 2, 3, and 4, and A is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

or

(2)X^1 is amino;

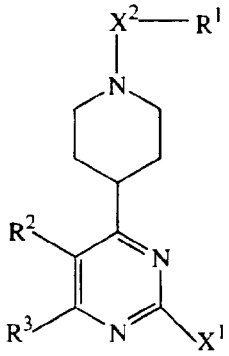
X^2 is carbonyl (-(CO)-);

R^1 is an C_{6-10} alkyl, a cycloalkyl, an aryl substituted by two or three halogen atoms, 2, 3-methylenedioxyphenyl, 3, 4-methylenedioxyphenyl, a C_{7-15} aralkyl or $-(CH_2)_m-$ A, wherein m is an integer selected from the group consisting of 6, 7, 8, 9, and 10, and A is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, carboxyl, an alkoxy, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl or a substituted aryl;

R^2 and R^3 are combined with the pyrimidine ring to form quinazoline, a substituted quinazoline, pyridopyrimidine, or a substituted pyridopyrimidine;

or a pharmaceutically acceptable salt thereof.

A preferred compound is represented by the formula (1-b);



(1-b)

wherein X^1 is amino;

X^2 is carbonyl (-(CO)-), carbonyloxy (-(CO)O-), or carbonylamino(-CONH-);

R^1 is an alkyl, a cycloalkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_m-$ A, wherein m is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and A is a halogen atom, a cycloalkyl, hydroxy, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

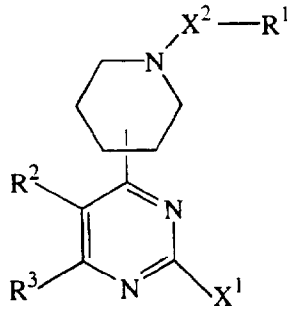
R^2 is hydrogen or an alkyl;

R^3 is an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-$ A', wherein m' is an integer selected from the group consisting of 1 and 2, and A' is an aryl, a substituted aryl or a heteroaryl;

or R^2 and R^3 are combined with the pyrimidine ring to form quinazoline, a substituted quinazoline, pyridopyrimidine or a substituted pyridopyrimidine;

or a pharmaceutically acceptable salt thereof.

A preferred compound is represented by formula (1-c),



(1-c)

wherein X^1 is amino or hydroxy;

X^2 is carbonyl (-(CO)-), carbonyloxy (-(CO)O-), carbonylamino (-(CO)NH-), or sulfonyl (-(SO_2)-);

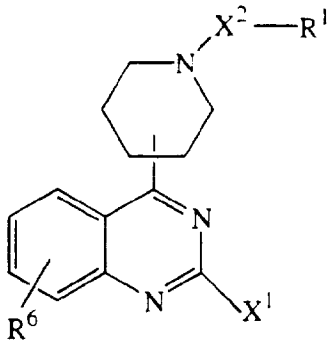
R^1 is an alkyl, a cycloalkyl, an aryl, a substituted aryl, a heteroaryl, or -$(CH_2)_m$- A, wherein m is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, and A is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkokycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

R^2 is hydrogen, an alkyl, or an aryl;

R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or -$(CH_2)_{m'}$- A', wherein m' is an integer selected from the group consisting of 1, 2, 3, and 4, and A' is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

or a pharmaceutically acceptable salt thereof.

A preferred compound is represented by formula (1-d),



(1-d)

wherein X^1 is amino;

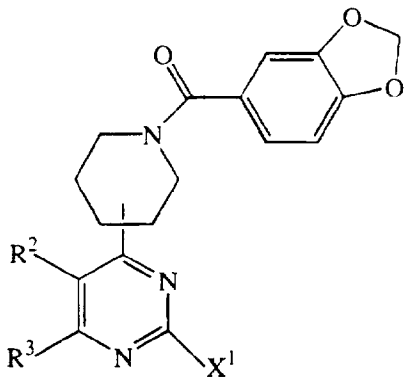
X^2 is carbonyl (-(CO)-);

R^1 is an C_{6-10} alkyl, a cycloalkyl, an aryl substituted by two or three halogen atoms, 2, 3-methylenedioxyphenyl, 3, 4-methylenedioxyphenyl, a C_{7-15} aralkyl or $-(CH_2)_m-$ A, wherein m is an integer selected from the group consisting of 6, 7, 8, 9, and 10, and A is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, carboxyl, an alkoxy, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl or a substituted aryl;

R^6 is a halogen atom, an alkyl, an alkoxy, nitro, cyano, carboxyl, hydroxyl, amino, trifluoromethyl, an alkylamino, a dialkylamino, an alkanoyl, an alkanoylamino, sulfamoyl, an alkylaminosulfonyl, a dialkylaminosulfonyl or an alkoxycarbonyl;

or a pharmaceutically acceptable salt thereof.

A more preferred compound is represented by formula (1-e),



(1-e)

wherein X^1 is amino or hydroxy;

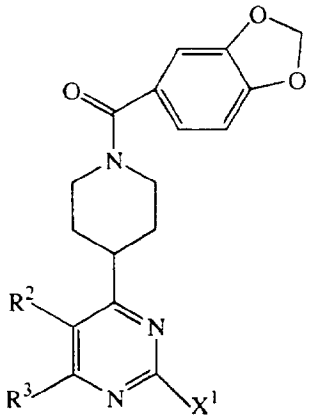
R^2 is hydrogen, an alkyl, or an aryl;

R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-$ A', wherein m' is an integer selected from the group consisting of 1, 2, 3 and 4, and A' is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

or R^2 and R^3 are combined with the pyrimidine ring to form quinazoline, a substituted quinazoline, a pyridopyrimidine or a substituted pyridopyrimidine;

or a pharmaceutically acceptable salt thereof.

A preferred embodiment included in the formula (1-e) is represented by the formula (1-f).



(1-f)

wherein X^1 is amino or hydroxy;

R^2 is hydrogen, an alkyl, or an aryl;

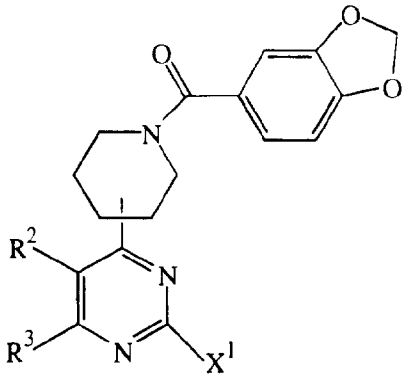
R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-A'$, wherein m' is an integer selected from the group consisting of 1, 2, 3 and 4, and A' is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

or R^2 and R^3 are combined together with the pyrimidine ring to form quinazoline, a substituted quinazoline, a pyridopyrimidine or a substituted pyridopyrimidine;

or a pharmaceutically acceptable salt thereof.

This invention also provides a method for inhibiting retrovirus long terminal repeat transcriptional activation in a patient in need of such inhibition, which comprises administering to a patient a pharmaceutically effective amount of a compound

represented by formula (1-e)



(1-e)

wherein X^1 is amino or hydroxy;

R^2 is hydrogen, an alkyl, or an aryl;

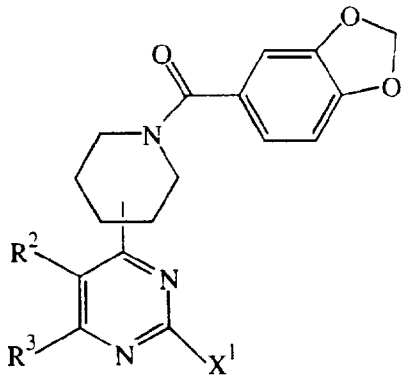
R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-$ A', wherein m' is an integer selected from the group consisting of 1, 2, 3 and 4, and A' is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

or R^2 and R^3 are combined with the pyrimidine ring to form quinazoline, a substituted quinazoline, a pyridopyrimidine or a substituted pyridopyrimidine;

or a pharmaceutically acceptable salt thereof.

This invention also provides a method for inhibiting human immunodeficiency virus-1 long terminal repeat transcriptional activation in a patient in need of such inhibition, which comprises administering to a

patient a pharmaceutically effective amount of a compound represented by formula (1-e)



(1-e)

wherein X^1 is amino or hydroxy;

R^2 is hydrogen, an alkyl, or an aryl;

R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-$ A', wherein m' is an integer selected from the group consisting of 1, 2, 3 and 4, and A' is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

or R^2 and R^3 are combined with the pyrimidine ring to form quinazoline, a substituted quinazoline, a pyridopyrimidine or a substituted pyridopyrimidine;

or a pharmaceutically acceptable salt thereof.

Best Mode for Carrying Out the Invention

The functional groups in the present invention represented by the formulae (1), (1-a), (1-b), (1-c), (1-

d), (1-e) and (1-f) are described below.

The term "alkyl" as used herein refers to a straight or branched chain hydrocarbon group having 1 to 10 carbon atoms. Examples of the alkyl are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonanyl, decanyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl and the like.

The term "C_{6-10}alkyl" as used herein refers to a straight chain hydrocarbon group having 6 to 10 carbon atoms. Examples of the C_{6-10}alkyl are hexyl, heptyl, octyl, nonanyl, decanyl, and the like.

The term "cycloalkyl" as used in herein refers to a saturated hydrocarbon group possessing at least one carbocyclic ring, the ring containing 3 to 7 carbon atoms. Examples of the cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl cyclohexyl and the like.

The term "alkenyl" as used herein refers to a hydrocarbon group having 2 to 10 carbon atoms possessing at least one double bond. Examples of the alkenyl are ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl 3-methyl-2-butenyl and the like.

The term "alkoxy" as used herein refers to a monovalent substituent comprising an alkyl group having 1 to 6 carbon atoms linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of

the alkoxy are methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy, pentyloxy, 1-methylbutoxy, 2-methylbutoxy, 3-methylbutoxy, 1,1-dimethylpropoxy, 1,2-dimethylpropoxy, 2,2-dimethylpropoxy, hexyloxy, 1-methylpentyloxy, 2-methylpentyloxy, 3-methylpentyloxy, 4-methylpentyloxy, 1,1-dimethylbutoxy, 1,2-dimethylbutoxy, 1,3-dimethylbutoxy, 2,2-dimethylbutoxy, 2,3-dimethylbutoxy, 3,3-dimethylbutoxy, 1-ethyl-1-methylpropoxy 1-ethyl-2-methylpropoxy and the like.

The term "alkylthio" refers to a monovalent substituent comprising an alkyl group having 1 to 6 carbon atoms linked through an ether sulfur having its free valence bond from the ether sulfur. The examples of the alkylthio are methylthio, ethylthio, propylthio, 1-methylethylthio, butylthio, 1-methylpropylthio, 2-methylpropylthio, pentylthio, 1-methylbutylthio, 2-methylbutylthio, 3-methylbutylthio, 1,1-dimethyl-propylthio, 1,2-dimethylpropylthio, 2,2-dimethyl-propylthio, hexylthio, 1-methylpentylthio, 2-methyl-pentylthio, 3-methylpentylthio, 4-methylpentylthio, 1,1-dimethylbutylthio, 1,2-dimethylbutylthio, 1,3-dimethylbutylthio, 2,2-dimethylbutylthio, 2,3-dimethylbutylthio, 3,3-dimethylbutylthio, 1-ethyl-1-methylpropylthio 1-ethyl-2-methylpropylthio and the like.

The term "alkoxycarbonyl" refers to a monovalent substituent having the formula alkyl-O-(C=O)-. Examples of the alkoxycarbonyl are methoxycarbonyl,

ethoxycarbonyl, propoxycarbonyl, 1-methylethoxycarbonyl, butoxycarbonyl, 1,1-dimethylethoxycarbonyl and the like.

The term "alkylamino" refers to a monosubstituted derivative of ammonia, wherein a hydrogen of ammonia is replaced by an alkyl group having 1 to 4 carbon atoms and examples of the alkylamino are methylamino, ethylamino, propylamino, 1-methylethylamino, butylamino, 1,1-dimethylethylamino and the like.

The term "dialkylamino" refers to a disubstituted derivative of ammonia, wherein two hydrogens of ammonia are replaced by alkyl groups having 1 to 4 carbon atoms and examples of the alkylamino are N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino, N-methyl-N-ethylamino, N,N-dibutylamino, N-methyl-N-(1,1-dimethylethyl)amino and the like.

The term "aryl" as used herein refers to an aromatic hydrocarbon possessing at least one hydrocarbon ring having up to 10 carbon atoms and examples of the aryl are phenyl, 1-naphthyl, 2-naphthyl and the like.

The term "aryloxycarbonyl" refers to a monovalent substituent having the formula aryl-O-(C=O)-. Examples of the group includes an aryloxycarbonyl group having 7 to 13 carbon atoms and is specifically exemplified by phenoxycarbonyl.

The term "alkyloxycarbonylamino" refers to a primary or secondary amine, which is replaced by a substituent having the formula alkyl-O-(C=O)- and examples of the alkyloxycarbonylamino are t-

butoxycarbonylamino and the like.

Examples of the halogen atom are fluorine, chlorine, bromine and iodine atoms.

The substituent of the substituted aryl may be at one or more of the carbons of the aromatic ring. If the aryl group has two or more substituents, the substituents may be same or different from each other. Examples of the substituent of the substituted aryl are a halogen atom, an alkyl, an alkoxy, nitro, cyano, carboxyl, hydroxy, amino, trifluoromethyl, an alkylamino, a dialkylamino, an alkanoyl, an alkanoylamino, sulfamoyl, an alkylaminosulfonyl, a dialkylaminosulfonyl, an alkoxycarbonyl and the like. Furthermore, the substituents adjacent to each other may be combined together to form an alkylenedioxy group such as 2,3-methylenedioxy, 3,4-methylenedioxy, 2,3-ethylenedioxy, 3,4-ethylenedioxy, or to form a heterocyclic group fused with an aryl ring such as 2,3-dihydrobenz[b]furan.

The term "alkanoyl" refers to the radical formed by removal of the hydroxyl function from a straight or branched alkanoic acid having 1 to 6 carbon atoms and examples are formyl, acetyl, propionyl, butyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and the like.

The term "alkanoylamino" refers to a primary or secondary amine, wherein a hydrogen of the amine is replaced by an alkanoyl group having 1 to 6 carbon atoms. Examples of the alkanoylamino are formylamino, acetylamino, propionylamino, butyrylamino, valerylamino,

isovalerylamino, pivaloylamino, hexanoylamino and the like.

The term "alkylaminosulfonyl" refers to a monovalent substituent comprising an alkylamino group linked through a sulfonyl group having its free valence bond from the sulfur atom and examples of the alkylaminosulfonyl are methylaminosulfonyl, ethylaminosulfonyl, propylaminosulfonyl, 1-methylethylaminosulfonyl, butylaminosulfonyl, 1,1-dimethylethylaminosulfonyl and the like.

The term "dialkylaminosulfonyl" refers to a monovalent substituent comprising an dialkylamino group linked through the sulfonyl group having its free valence bond from the sulfur atom and examples of the dialkylaminosulfonyl are N,N-dimethylaminosulfonyl, N,N-diethylaminosulfonyl, N,N-dipropylaminosulfonyl, N-methyl-N-ethylaminosulfonyl, N,N-dibutylaminosulfonyl, N-methyl-N-(1,1-dimethylethyl)aminosulfonyl and the like.

The term "heteroaryl" refers to a unsaturated aromatized heterocyclic group such as a monocyclic or bicyclic heteroaryl group comprising not more than 9 carbon atoms, and 1 to 3 hetero atom(s) selecting from the group of nitrogen, oxygen and sulfur atoms, which may be the same or different. Examples of heteroaryl are 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothiazolyl,

4-isothiazolyl, 5-isothiazolyl, 2-furyl, 3-furyl, 2-imidazolyl, 4-imidazolyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-pyrazinyl, 3-pyridazinyl, 4-pyridazinyl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 3-oxadiazolyl, 5-oxadiazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 4-benzo[b]furan, 5-benzo[b]furan, 6-benzo[b]furan, 7-benzo[b]furan, 4-benzimidazole, 5-benzimidazole, 4-benzothiazole, 5-benzothiazole, 6-benzothiazole, 7-benzothiazole, 4-benzoxazole, 5-benzoxazole, 6-benzoxazole, 7-benzoxazole and the like.

The term "saturated heterocyclic" refers to a monocyclic saturated heterocyclic group comprising not more than 6 carbon atoms and one or two hetero atom(s) selecting from the group of nitrogen, oxygen and sulfur atoms, which may be the same or different, and preferred embodiments include a 5- or 6-membered saturated heterocyclic. Examples of the 5-membered saturated heterocyclic group are 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-oxoranyl, 3-oxoranyl, 2-thioranyl and 3-thioranyl. Examples of the 6-membered saturated heterocyclic group are piperidino, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 2-piperazinyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, morpholino, 2-morpholinyl, 3-morpholinyl and the like.

The monocyclic saturated heterocyclic group may

be substituted with an alkyl.

The aromatic group fused together with the pyrimidine ring forms a group having a benzopyrimidine (quinazoline) structure. The fused aromatic group may be substituted with a substituent(s) such as a halogen atom, an alkyl, an alkoxy, nitro, cyano, carboxyl, hydroxy, amino, trifluoromethyl, an alkylamino, a dialkylamino, an alkanoyl, an alkanoylamino, sulfamoyl, an alkylamino-sulfonyl, a dialkylaminosulfonyl, an alkoxycarbonyl and the like.

The heteroaryl group fused with the pyrimidine ring forms a group having a pyridopyrimidine structure. Specific examples of such a group include pyrido[2,3-d]pyrimidine, pyrido[3,4-d]pyrimidine, pyrido[4,3-d]pyrimidine and pyrido[3,2-d]pyrimidine. The 5, 6, 7 and 8 positions may be substituted by a substituent such as a halogen atom, an alkyl, an alkoxy, nitro, cyano, carboxyl, hydroxy, amino, trifluoromethyl, an alkylamino, a dialkylamino, an alkanoyl, an alkanoylamino, sulfamoyl, an alkylaminosulfonyl, a dialkylaminosulfonyl, an alkoxycarbonyl and the like.

Examples of the pharmaceutically acceptable salt of the invention are a salt with a mineral acid such as hydrogen chloride, hydrogen bromide, sulfuric acid phosphoric acid and the like; a salt with an organic carboxylic acid such as formic acid, acetic acid, fumaric acid, maleic acid, malic acid, tartaric acid, aspartic

acid, glutamic acid and the like; a salt with a sulfonic acid such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, hydroxybenzenesulfonic acid, dihydroxybenzenesulfonic acid and the like; a salt with an alkali metal such as sodium, potassium and the like; a salt with an alkaline earth metal such as calcium, magnesium and the like; a salt with an organic base such as trimethylamine, triethylamine, pyridine, ammonia salts and the like.

The compound of the present invention may have a tautomeric isomer, a stereoisomer, a geometrical isomer or an optical isomer. The present invention include these isomers.

The compound of the present invention may have hydrates, solvates or crystalline forms. The present invention also includes these forms.

This invention provides a method of treatment of or a pharmaceutical composition for treating a patient having a high concentration of TNFα in blood and/or tissue, such as in septic shock, osteoarthritis, multiple sclerosis, inflammatory bowel diseases such as ulcerative colitis or Crohn's disease, Behçet disease, systemic lupus erythematosus (SLE), graft versus host disease (GvHD), multiple organ failure, malaria, meningitis, hepatitis, non-insulin-dependent diabetes mellitus, asthma, adult respiratory distress syndrome (ARDS), tuberculosis, atherosclerosis, Alzheimer's disease and

the like, by administering an effective amount of a compound represented by the formula (1), (1-a), (1-b), (1-c), (1-d), (1-e) or (1-f).

The method for treatment or pharmaceutical composition can be applied for not only limited to human but mammals or animals.

This invention also provide a method of inhibiting retrovirus long terminal repeat transcriptional activation in a mammal or an animal in need of such inhibition comprises administering to the mammal or animal, a pharmaceutically effective amount of a compound of the invention represented by the formula (1-e) or (1-f).

Examples of the above retrovirus are HIV-I (human immunodeficiency virus-1), HTLV-I (human adult T-cell leukemia-I virus), HTLV-II (human adult T-cell leukemia-II virus), ALV (avian leukemia virus), RSV (Rous sarcoma virus), Mason-Phizer mammary tumor-associated virus, simian T-cell lymphotropic virus type I, simian T-cell lymphotropic virus type III, feline leukemia virus, equine infectious anemia virus, caprine arthritis encephalitis virus and the like.

The pharmaceutical composition of the present invention can be administered by conventional dosage

forms such as oral, parenteral (including intramuscular, subcutaneous and intravenous), rectal, nasal, topical, implant and the like. The formulations may, where appropriate, be prepared by any of the methods well known in the art of pharmaceutics. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into a desired formulation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, capsules(each of which includes sustained release or timed release formulations,), pills, powders, cachets, suppositories and the like. Examples of liquid oral dosage forms are solutions, suspensions and the like. Examples of parenteral preparations are sterile solutions, suspensions, and the like prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose, etc.); fillers (e.g. lactose, microcrystalline cellulose, calcium phosphate, etc.); lubricants (e.g. magnesium stearate, talc, silica, etc.); disintegrants (e.g. potato starch, sodium starch glycollate, etc.); or wetting agents (e.g. sodium lauryl sulphate etc.).

Liquid preparations for oral administration may take the form of, for example, solutions, syrups, or suspensions, or they may be presented as a dry product

for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutical acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats, etc.); emulsifying agents (e.g. lectin, acacia, etc.); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol, etc.); and preservatives (e.g. methyl or propyl-, p-hydroxybenzoates, sorbic acid, etc.).

For topical administration, the pharmaceutical compositions may take the form of buccal or sublingual tablets, drops or lozenges formulated in a conventional manner.

For topical administration to the epidermis, the compounds may be formulated as creams, gels, ointments, lotions or as transdermal patches. Such compositions may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening, gelling, emulsifying, stabilizing, dispersing, suspending, and/or coloring agents.

The active compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramusculary) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly

soluble derivatives, for example as a sparingly soluble salt.

The active compounds of the invention may be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or multi-dose containers, with added preservatives. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions, such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

For intranasal administration the active compounds may be used, for example, as a liquid spray, as a powder or in the form of drops.

For administration by inhalation the active compounds are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane,

dichlorotetrafluoroethane, 1,1,1,2-terafluoroethane, carbon dioxide or other suitable gas. In the case of pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of an active compound of the invention and a suitable powder base such as lactose or starch.

A convenient unit dose formulation contains the active ingredient in an amount of from about 1 to about 1000 mg.

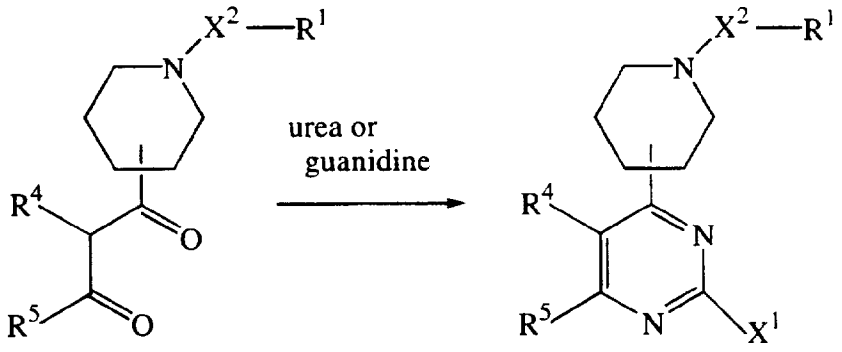
Any of the pharmaceutical compositions described above may be presented in a conventional manner associated with controlled release forms.

It will be appreciated that the amount of a compound of the formula (1), (1-a), (1-b), (1-c), (1-d), (1-e), or (1-f) required for use in treatment will vary not only with the particular compound selected, but also with the route of administration, the nature of the condition being treated and the age, weight and condition of the patient and ultimately be at the discretion of the attendant physician or veterinarian. In general, the daily dose of the active compound of the invention for adult is selected from the range of from about 10 to about 1000 mg, preferably about 10 to about 500 mg for oral administration and, or from the range of from about 1 to about 100 mg, by single administration or by

dividing the dose several times.

The piperidinylpyrimidine derivatives of the present invention may be prepared, e.g., by the following processes.

Process (A)



(3) (2)

wherein:

X^1, X^2 and R^1 have the same meaning as defined in the formula 1;

R^4 is hydrogen atom, an alkyl or an aryl; and,

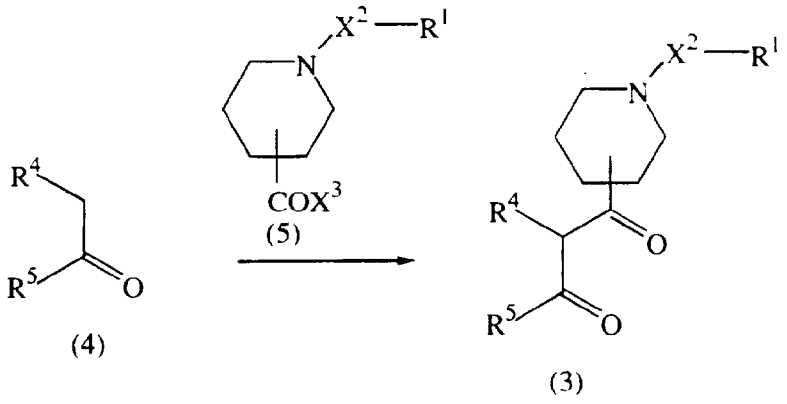
R^5 is an alkyl group, an aryl, a heteroaryl or a group represented by the formula: $-(CH_2)_{m'}-A'$, wherein m' and A' have the same meaning as defined in the formula (1).

A compound represented by the formula (2) is included by the formula (1). The compound represented by the formula (2) may be prepared by treating a 1,3-diketone compound represented by the formula (3) with urea or guanidine either in the presence or absence of a base. The reaction may be carried out either in the absence or presence of an inert solvent at a temperature

ranging from about room temperature to about 200°C. In the reaction above, examples of the base are an alkali metal alkoxide such as potassium t-butoxide, sodium methoxide, sodium ethoxide and the like; an alkali metal hydride such as sodium hydride and the like; an organic base such as triethylamine, pyridine, 4-dimethylamino-pyridine, N-methylmorpholine and the like; an inorganic salt such as potassium carbonate, sodium carbonate, sodium hydrogen carbonate and the like; and the like.

Examples of the inert solvent are an alcohol such as methanol, ethanol, t-butanol and the like; an aprotonic solvent such as pyridine, N,N-dimethylformamide dimethylsulfoxide, hexamethylphosphoramide, acetonitrile and the like; a halogenated hydrocarbon such as dichloromethane, chloroform, 1,2-dichloroethane and the like; a hydrocarbon such as benzene, toluene, hexane and the like; and an ether such as tetrahydrofuran, dioxane, diethyl ether and the like; and the like.

The starting compound represented by the formula (3) may be prepared by reacting a ketone derivatives represented by the formula (4) with an acid chloride or an ester represented formula (5):



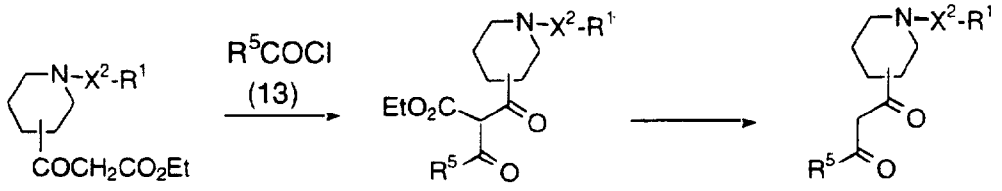
wherein X^2, R^1, R^4 and R^5 have the same meaning as defined in the formula (2) and X^3 is chlorine atom or an alkoxy.

The reaction may be carried out in the presence of a base in an inert solvent at a temperature ranging from about -78°C to about reflux temperature. Examples of the base are an alkali metal alkoxide such as potassium t-butoxide, sodium methoxide sodium ethoxide and the like; a lithium compound such as n-butyl lithium, lithium N,N-diisopropylamide and the like; a metal hydride such as sodium hydride and the like; and the like.

Examples of the solvents are an alcohol such as methanol, ethanol, t-butanol and the like; an ether such as diethyl ether, tetrahydrofuran and the like; and the like.

The starting compounds (5) may be prepared from isonipecotic acid, nipecotic acid, pipecolinic acid or a derivative thereof by a conventional method known to a skilled person in the art of organic chemistry.

A 1,3-diketone compound may also be prepared by the following processes.



(12) (14) (15)

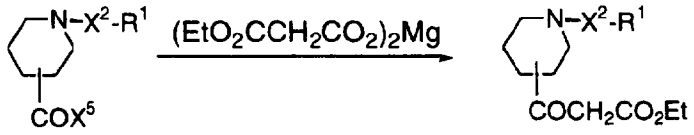
Wherein X^2 and R^5 are as defined in the formula (2).

The compound of the formula (14) may be prepared by treating a β-ketoester of the formula (12) with an acid chloride of the formula (13). The reaction is carried out in the presence of a suitable base such as an alkaline metal hydride (e.g. sodium hydride, etc.), or an alkaline earth metal alkoxide (e.g. magnesium ethoxide, etc.) in an inert solvent such as an aprotonic solvent (e.g. N,N-dimethylformamide, dimethylsulfoxide, etc.), an ether (e.g. tetrahydrofuran, diethylether, etc.) or a hydrocarbon (e.g. benzene, toluene, hexane, etc.), at a temperature ranging from about 0°C to about reflux temperature of the solvent.

The acid chloride (13) may be prepared by treating the corresponding acid with a chlorinating agent using the reactions and techniques well known to a skilled person in the art of organic chemistry. Selected examples of the chlorinating agent include but are not limited to oxalyl chloride, thionyl chloride, phosphorous oxychloride, phosphorous trichloride, and phosphprous pentachloride. The reaction may be carried out either in

the absence of solvent or in an inert solvent such as a halogenated hydrocarbon (e.g. dichloromethane, dichloroethane, etc.), an ether (e.g. diethylether, tetrahydrofuran, etc.), or hydrocarbon (e.g. benzene, toluene, hexane, etc.), at a temperature ranging from about 0°C to about reflux temperature of the solvent either in the absence or presence of base. Selected examples of the base include but are not limited to pyridine, 4-dimethylaminopyridine, triethylamine and imidazole.

The compound of the formula (15) may be prepared by deesterizing the compound of formula (14). The deesterizing reaction may be carried out in a solvent such as an aprotonic solvent (e.g. N,N-dimethylformamide, dimethylsulfoxide, etc.), or an acidic solvent (e.g. acetic acid, etc.) either in the presence or absence of water at a temperature ranging from about room temperature to about reflux temperature.



(11) (12)

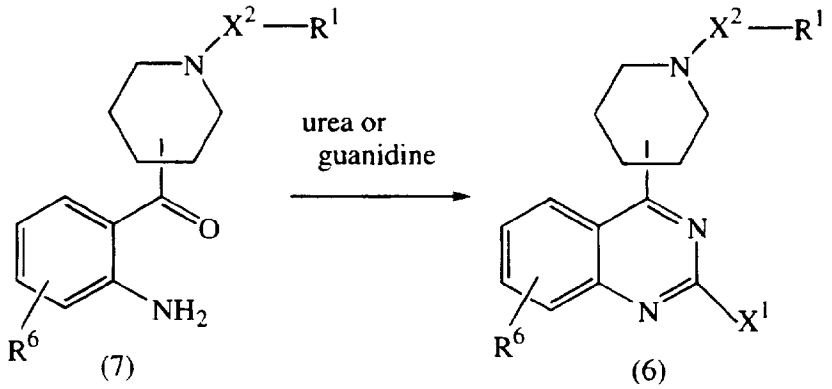
(Wherein X^2 and R^1 have the same meaning described in the formula (2). X^5 is a chlorine atom, imidazole or a alkoxycarbonyloxy.)

The β-ketoester of the formula (12) may be prepared by treating an isonipecotic acid derivative of

the formula (11) with magnesium monoethylmalonate. The reaction is carried out in an inert solvent such as an aprotonic solvent (e.g. N,N-dimethylformamide, dimethylsulfoxide, etc.), an ether (e.g. tetrahydrofuran, diethylether, etc.), or a hydrocarbon (e.g. benzene, toluene, hexane, etc.), at a temperature ranging from about 0°C to about reflux temperature of the solvent.

Process (B)

With respect to a compound within the formula (1) wherein R^2 and R^3 are combined with pyrimidine to form a pyridopyrimidine or a quinazoline, the process may be explained by using an example compound of formula (6) having the quinazoline structure.



wherein:

X^1, X^2 and R^1 have the same significance as defined in the formula (1-d);

R^6 represents a substituent at the 5, 6, 7 or 8 position of the quinazoline ring. The compound (6) may have one R^6 or up to 4 R^6's. If the compound (6) has more than two R^6's, each R^6's may be the same or different. R^6 is a

halogen, an alkyl, an alkoxy, nitro, cyano, carboxyl, hydroxy, amino, trifluoromethyl, an alkylamino, a dialkylamino, an alkanoyl, an alkanoylamino, sulfamoyl, an alkylaminosulfonyl, a dialkylamino or an alkoxycarbonyl.

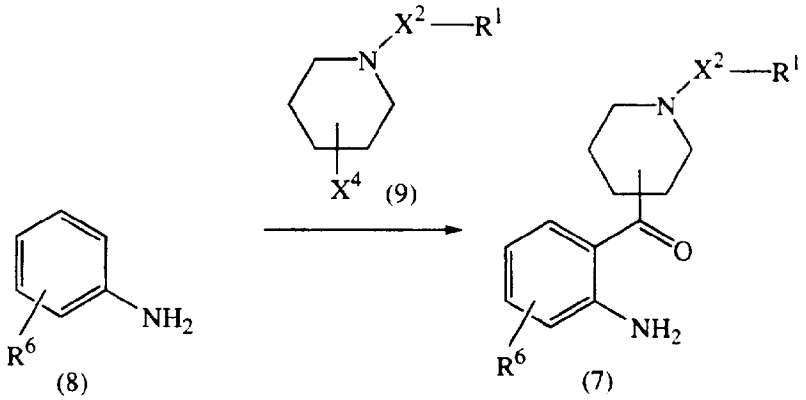
A compound of the formula (6) may be prepared by treating an aminoketone compound represented by the formula (7) with a reagent such as urea, sodium cyanate, potassium cyanate, guanidine or cyanamide. The reaction may be carried out either in the absence or presence of an inert solvent, either in the presence or absence of a base, at a temperature ranging from about room temperature to about 200°C.

In the reaction described above, examples of the base are an alkali metal alkoxide such as potassium t-butoxide, sodium methoxide, sodium ethoxide and the like; a metal hydride such as sodium hydride and the like; an organic amine such as triethylamine, pyridine, 4-dimethylaminopyridine, N-methylmorpholine and the like; an inorganic salt such as potassium carbonate, sodium carbonate, sodium hydrogencarbonate and the like; and the like.

Examples of the solvent are an alcohol such as methanol, ethanol, t-butanol and the like; an aprotonic polar solvent such as pyridine, N,N-dimethylformamide, dimethylsulfoxide, hexamethylphosphoramide, acetonitrile and the like; a halogenated hydrocarbon such as dichloromethane, chloroform, 1,2-dichloroethane and the

like; a hydrocarbon such as benzene, toluene, hexane and the like; an ether such as tetrahydrofuran, dioxane, diethyl ether and the like; and the like.

The starting compounds (7) may be prepared by treating an aniline derivative of the formula (8) with a nitrile or an acid chloride of the formula (9).



wherein X^2, R^1 and R^6 have the same meaning as defined in the formula (1-d) and X^4 is cyano or -COCl. The reaction may be carried out in an inert solvent in the presence of a Lewis acid at a temperature ranging from about room temperature to about reflux temperature.

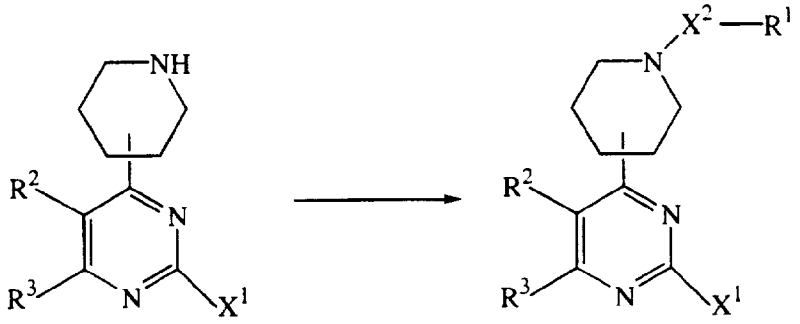
Examples of the Lewis acid are aluminum chloride, tin tetrachloride, titanium tetrachloride, zinc dichloride, boron trichloride and the like. Two or more Lewis acids in combination may be applied to accelerate the reaction.

Examples of the solvent are a halogenated hydrocarbon such as dichloromethane, chloroform, 1,2-dichloroethane and the like; a hydrocarbon such as benzene, toluene, hexane and the like; an ether such as

tetrahydrofuran, dioxane, diethyl ether and the like; carbon disulfide; and the like.

The starting compounds (9) may be prepared from isonipecotinic acid, nipecotic acid, pipecolinic acid or a derivative thereof by a method well known to a skilled person in the art of organic chemistry.

Process (C)



(10) (1)

wherein X^1, X^2, R^1, R^2 and R^3 have the same meaning as defined in the formula (1).

The piperidinylpyrimidine derivative of the formula (1) may be prepared by introducing the corresponding substituent into a piperidine compound of the formula (10).

A compound of formula (1), wherein X^2 is -(CO)-, may be prepared by treating a compound of the formula (10) with a corresponding acid anhydride or acid chloride. The reaction may be carried out in an inert solvent in the presence of a condensing reagent at a temperature ranging from about 0°C to about reflux temperature.

A compound of formula (1), wherein X^2 is -(CO)-, may also be prepared by treating a compound of the formula (10) with a corresponding acid. The reaction may be carried out in an inert solvent in the presence of a condensing reagent at a temperature ranging from about 0°C to about reflux temperature.

A compound of formula (1), wherein X^2 is -(CO)O-, may be prepared by treating a compound of the formula (10) with a corresponding chloroformate. The reaction may be carried out in an inert solvent in the presence of a base at a temperature ranging from about 0°C to about reflux temperature.

A compound of formula (1), wherein X^2 is -(CO)NH-, may be prepared by treating a compound of the formula (10) with a corresponding isocyanate. The reaction may be carried out in an inert solvent at a temperature ranging from about 0°C to about reflux temperature.

A compound of formula (1), wherein X^2 is $-(SO_2)-$, may be prepared by treating a compound of the formula (10) with a corresponding sulfonic acid chloride. The reaction may be carried out in an inert solvent in the presence of a base at a temperature ranging from about 0°C to about reflux temperature.

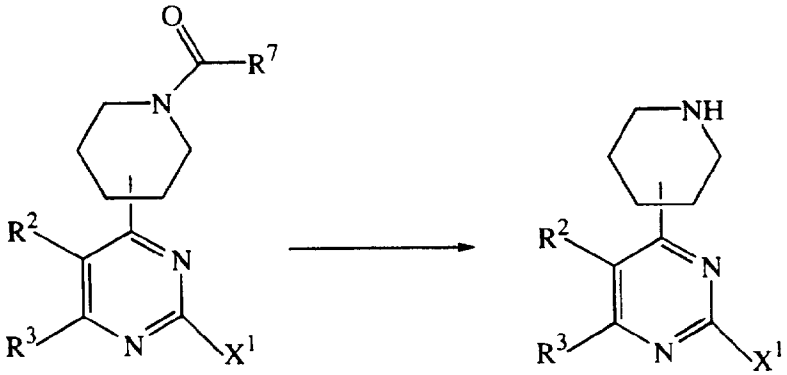
In the reaction described above, examples of the base are an organic amine such as triethylamine, pyridine, 4-dimethylaminopyridine, N-methylmorpholine and

the like; an inorganic salt such as potassium carbonate, sodium carbonate, sodium hydrogen carbonate and the like; and the like.

Examples of the solvent are an aprotonic polar solvent such as N,N-dimethylformamide, dimethylsulfoxide, hexamethylphosphoramide, acetonitrile and the like; a hydrocarbon such as benzene, toluene, hexane and the like; a halogenated hydrocarbon such as dichloromethane, chloroform, 1,2-dichloroethane and the like; an ether such as tetrahydrofuran, dioxane, diethyl ether and the like; and the like.

Examples of the condensing reagent are N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and the like.

The compound of formula (10) may be prepared by hydrolyzing a compound of formula (11):



(11) (10)

wherein X^1, R^2 and R^3 have the same meaning as defined in the formula (1) and R^7 is an alkyl or an aryl.

The hydrolysis above may be carried out in a

solvent mixture of an aqueous solution of potassium hydroxide or sodium hydroxide and an alcohol such as ethanol, ethylene glycol or methoxyethanol, or an ether such as 1,4-dioxane or tetrahydrofuran, at a temperature ranging from about room temperature to about the reflux temperature.

In the reactions described above, where the substituent R^1, R^2, R^3, R^4 or R^5 may contain a residue such as amino, an alkyl amino or hydroxy, the residue may be protected prior to the reaction and the protective group is then deprotected to prepare the desired compound. A man skilled in the art of organic chemistry may choose an appropriate protective group from groups described below depending on the nature or condition of reactions or processes. Examples of the protective group available are an alkanoyl such as acetyl, benzoyl and the like for protecting the amino and alkylamino groups, an alkanoyl such as acetyl, benzoyl and the like, alloyl, benzyl, methyl, methoxymethyl, trimethylsilyl and the like for protecting the hydroxy group. The details of the protective groups and procedures are described in T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley & Sons Inc. (1981).

Following are typical compounds of the invention, wherein the symbol "Ph" is phenyl and "Boc" is t-butoxycarbonyl.

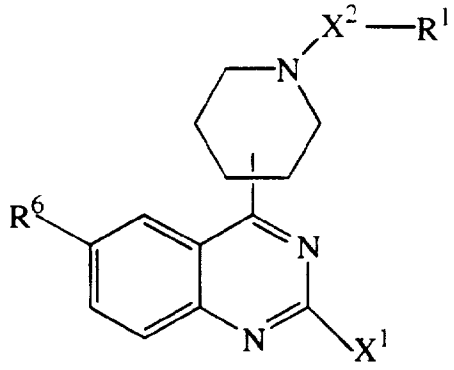


Table 1

X^2	R^2	R^6	X^2	R^2	R^6
CO	cyclohexyl	H	CO	2-fluorophenyl	H
	cyclohexylmethyl			3-fluorophenyl	
	$-CH_3$			4-fluorophenyl	
	$-CH_2CH_3$			2-methylphenyl	
	$-(CH_2)_2CH_3$			3-methylphenyl	
	$-(CH_2)_3CH_3$			4-methylphenyl	
	$-(CH_2)_4CH_3$			2-furyl	
	$-(CH_2)_5CH_3$			3-furyl	
	$-(CH_2)_6CH_3$			2-pyridyl	
	$-(CH_2)_7CH_3$			3-pyridyl	
	$-(CH_2)_8CH_3$			4-pyridyl	
	$-(CH_2)_9CH_3$			2,3-dimethoxy-phenyl	
	$-(CH_2)_5OH$			2,4-dimethoxy-phenyl	
	$-(CH_2)_6OH$			2,5-dimethoxy-phenyl	
	$-(CH_2)_7OH$			2,6-dimethoxy-phenyl	
	$-(CH_2)_8OH$			3,4-dimethoxy-phenyl	
	$-(CH_2)_9OH$			3,5-dimethoxy-phenyl	
	phenyl			2,3-dichlorophenyl	
	2-methoxyphenyl			2,4-dichloropheny	
	3-methoxyphenyl			2,5-dichlorophenyl	
	4-methoxyphenyl			2,6-dichlorophenyl	
	2-chlorophenyl			3,4-dichlorophenyl	
	3-chlorophenyl			2,4-dinitrophenyl	
	4-chlorophenyl			3,4-methylene-dioxyphenyl	

(continued)

X^2	R^1	R^6	X^2	R^1	R^6
CO	2,3-methylene-dioxyphenyl	H	CO	2,5-dimethoxybenzyl	H
	1-naphthyl			3,4-dimethoxybenzyl	
	2-naphthyl			3,5-dimethoxybenzyl	
	2,3,4-trimethoxy-phenyl			2,4-dichlorobenzyl	
	2,3,6-trimethoxy-phenyl			2,6-dichlorobenzyl	
	2,4,5-trimethoxy-phenyl			3,4-dichlorobenzyl	
	2,4,6-trimethoxy-phenyl			2,4-dinitrobenzyl	
	3,4,5-trimethoxy-phenyl			3,4-methylenedioxy-benzyl	
	2,3,5-trichloro-phenyl			2,3-methylenedioxy-benzyl	
	2,4,6-trichloro-phenyl			3,4,5-trimethoxy-benzyl	
	benzyl			2-phenylethyl	
	2-methoxybenzyl			2-(2-methoxyphenyl)-ethyl	
	3-methoxybenzyl			2-(3-methoxyphenyl)-ethyl	
	4-methoxybenzyl			2-(4-methoxyphenyl)-ethyl	
	2-chlorobenzyl			2-(2,3-dimethoxy-phenyl)ethyl	
	3-chlorobenzyl			2-(3,4-dimethoxy-phenyl)ethyl	
	4-chlorobenzyl				
	2-fluorobenzyl				
	3-fluorobenzyl			2-(2,3,4-trimethoxy-phenyl)ethyl	
	4-fluorobenzyl				
	2-methylbenzyl			2-(3,4,5-trimethoxy-phenyl)ethyl	
	3-methylbenzyl				
	4-methylbenzyl			2-(2-chlorophenyl)-ethyl	
	2-pyridylmethyl			2-(4-chlorophenyl)-ethyl	
	3-pyridylmethyl				

(continued)

X^2	R^2	R^6	X^2	R^2	R^6
CO	2-(3,4-dichloro-phenyl)ethyl	H	SO_2	$-(CH_2)_7CH_3$	H
	2-(3,4-methylene-dioxyphenyl)ethyl			-Ph	
	3-phenylpropyl			$-CH_2Ph$	
	3-(4-methoxy-phenyl)propyl				
	3-(3,4-dimethoxy-phenyl)propyl				
	3-(3,4-methylene-dioxyphenyl)propyl				
(CO)O	Ph				
	$-CH_2Ph$				
(CO)NH	$-(CH_2)_7CH_3$				
	-Ph				
	$-CH_2Ph$				

(Continued)

X^2	R^5	R^6	X^2	R^5	R^6
CO	cyclohexyl	OCH_3	CO	2-fluorophenyl	OCH_3
	cyclohexylmethyl			3-fluorophenyl	
	$-CH_3$			4-fluorophenyl	
	$-CH_2CH_3$			2-methylphenyl	
	$-(CH_2)_2CH_3$			3-methylphenyl	
	$-(CH_2)_3CH_3$			4-methylphenyl	
	$-(CH_2)_4CH_3$			2-furyl	
	$-(CH_2)_5CH_3$			3-furyl	
	$-(CH_2)_6CH_3$			2-pyridyl	
	$-(CH_2)_7CH_3$			3-pyridyl	
	$-(CH_2)_8CH_3$			4-pyridyl	
	$-(CH_2)_9CH_3$			2,3-dimethoxyphenyl	
	$-(CH_2)_5OH$			2,4-dimethoxyphenyl	
	$-(CH_2)_6OH$			2,5-dimethoxyphenyl	
	$-(CH_2)_7OH$			2,6-dimethoxyphenyl	
	$-(CH_2)_8OH$			3,4-dimethoxyphenyl	
	$-(CH_2)_9OH$			3,5-dimethoxyphenyl	
	phenyl			2,3-dichlorophenyl	
	2-methoxyphenyl			2,4-dichlorophenyl	
	3-methoxyphenyl			2,5-dichlorophenyl	
	4-methoxyphenyl			2,6-dichlorophenyl	
	2-chlorophenyl			3,4-dichlorophenyl	
	3-chlorophenyl			2,4-dinitrophenyl	
	4-chlorophenyl			3,4-methylenedioxyphenyl	

(continued)

X^2	R^1	R^6	X^2	R^1	R^6
CO	2,3-methylene-dioxyphenyl	OCH_3	CO	2,5-dimethoxybenzyl	OCH_3
	1-naphthyl			3,4-dimethoxybenzyl	
	2-naphthyl			3,5-dimethoxybenzyl	
	2,3,4-trimethoxy-phenyl			2,4-dichlorobenzyl	
	2,3,6-trimethoxy-phenyl			2,6-dichlorobenzyl	
	2,4,5-trimethoxy-phenyl			3,4-dichlorobenzyl	
	2,4,6-trimethoxy-phenyl			2,4-dinitrobenzyl	
	3,4,5-trimethoxy-phenyl			3,4-methylenedioxy-benzyl	
	2,3,5-trichloro-phenyl			2,3-methylenedioxy-benzyl	
	2,4,6-trichloro-phenyl			3,4,5-trimethoxy-benzyl	
	benzyl			2-phenylethyl	
	2-methoxybenzyl			2-(2-methoxy-phenyl)ethyl	
	3-methoxybenzyl			2-(3-methoxy-phenyl)ethyl	
	4-methoxybenzyl			2-(4-methoxy-phenyl)ethyl	
	2-chlorobenzyl			2-(2,3-dimethoxy-phenyl)ethyl	
	3-chlorobenzyl			2-(3,4-dimethoxy-phenyl)ethyl	
	4-chlorobenzyl				
	2-fluorobenzyl				
	3-fluorobenzyl			2-(2,3,4-trimethoxy-phenyl)ethyl	
	4-fluorobenzyl				
	2-methylbenzyl			2-(3,4,5-trimethoxy-phenyl)ethyl	
	3-methylbenzyl				
	4-methylbenzyl			2-(2-chlorophenyl)-ethyl	
	2-pyridylmethyl			2-(4-chlorophenyl)-ethyl	
	3-pyridylmethyl				

(continued)

X^2	R^1	R^6	X^2	R^1	R^6
CO	2-(3,4-dichloro-phenyl)ethyl	OCH_3	SO_2	$-(CH_2)_7CH_3$	OCH_3
	2-(3,4-methylene-dioxyphenyl)ethyl			-Ph	
	3-phenylpropyl			$-CH_2Ph$	
	3-(4-methoxy-phenyl)propyl				
	3-(3,4-dimethoxy-phenyl)propyl				
	3-(3,4-methylene-dioxyphenyl)propyl				
(CO)O	Ph				
	$-CH_2Ph$				
(CO)NH	$-(CH_2)_7CH_3$				
	-Ph				
	$-CH_2Ph$				

(Continued)

X^2	R^1	R^6	X^2	R^1	R^6
CO	cyclohexyl	Cl	CO	2-fluorophenyl	Cl
	cyclohexylmethyl			3-fluorophenyl	
	$-CH_3$			4-fluorophenyl	
	$-CH_2CH_3$			2-methylphenyl	
	$-(CH_2)_2CH_3$			3-methylphenyl	
	$-(CH_2)_3CH_3$			4-methylphenyl	
	$-(CH_2)_4CH_3$			2-furyl	
	$-(CH_2)_5CH_3$			3-furyl	
	$-(CH_2)_6CH_3$			2-pyridyl	
	$-(CH_2)_7CH_3$			3-pyridyl	
	$-(CH_2)_8CH_3$			4-pyridyl	
	$-(CH_2)_9CH_3$			2,3-dimethoxy-phenyl	
	$-(CH_2)_5OH$			2,4-dimethoxy-phenyl	
	$-(CH_2)_6OH$			2,5-dimethoxy-phenyl	
	$-(CH_2)_7OH$			2,6-dimethoxy-phenyl	
	$-(CH_2)_8OH$			3,4-dimethoxy-phenyl	
	$-(CH_2)_9OH$			3,5-dimethoxy-phenyl	
	phenyl			2,3-dichlorophenyl	
	2-methoxyphenyl			2,4-dichlorophenyl	
	3-methoxyphenyl			2,5-dichlorophenyl	
	4-methoxyphenyl			2,6-dichlorophenyl	
	2-chlorophenyl			3,4-dichlorophenyl	
	3-chlorophenyl			2,4-dinitrophenyl	
	4-chlorophenyl			3,4-methylene-dioxyphenyl	

(continued)

X^2	R^5	R^6	X^2	R^5	R^6
CO	2,3-methylene-dioxyphenyl	Cl	CO	2,5-dimethoxy-benzyl	Cl
	1-naphthyl			3,4-dimethoxy-benzyl	
	2-naphthyl			3,5-dimethoxy-benzyl	
	2,3,4-trimethoxy-phenyl			2,4-dichloro-benzyl	
	2,3,6-trimethoxy-phenyl			2,6-dichloro-benzyl	
	2,4,5-trimethoxy-phenyl			3,4-dichloro-benzyl	
	2,4,6-trimethoxy-phenyl			2,4-dinitrobenzyl	
	3,4,5-trimethoxy-phenyl			3,4-methylene-dioxybenzyl	
	2,3,5-trichloro-phenyl			2,3-methylene-dioxybenzyl	
	2,4,6-trichloro-phenyl			3,4,5-trimeth-oxybenzyl	
	benzyl			2-phenylethyl	
	2-methoxybenzyl			2-(2-methoxy-phenyl)ethyl	
	3-methoxybenzyl			2-(3-methoxy-phenyl)ethyl	
	4-methoxybenzyl			2-(4-methoxy-phenyl)ethyl	
	2-chlorobenzyl			2-(2,3-dimethoxy-phenyl)ethyl	
	3-chlorobenzyl			2-(3,4-dimethoxy-phenyl)ethyl	
	4-chlorobenzyl				
	2-fluorobenzyl				
	3-fluorobenzyl			2-(2,3,4-trimeth-oxyphenyl)ethyl	
	4-fluorobenzyl				
	2-methylbenzyl			2-(3,4,5-trimeth-oxyphenyl)ethyl	
	3-methylbenzyl				
	4-methylbenzyl			2-(2-chloro-phenyl)ethyl	
	2-pyridylmethyl			2-(4-chloro-phenyl)ethyl	
	3-pyridylmethyl				

(continued)

X^2	R^1	R^6	X^2	R^1	R^6
CO	2-(3,4-dichloro-phenyl)ethyl	Cl	SO_2	$-(CH_2)_7CH_3$	Cl
	2-(3,4-methylene-dioxyphenyl)ethyl			-Ph	
	3-phenylpropyl			$-CH_2Ph$	
	3-(4-methoxy-phenyl)propyl				
	3-(3,4-dimethoxy-phenyl)propyl				
	3-(3,4-methylene-dioxyphenyl)propyl				
(CO)O	Ph				
	$-CH_2Ph$				
(CO)NH	$-(CH_2)_7CH_3$				
	-Ph				
	$-CH_2Ph$				

(Continued)

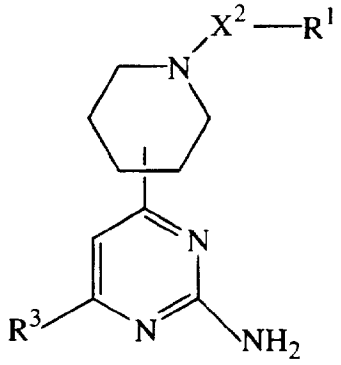


Table 2

X^2	R^1	R^3	X^2	R^1	R^3
CO	cyclohexyl	Ph	CO	2-fluorophenyl	Ph
	cyclohexylmethyl			3-fluorophenyl	
	$-CH_3$			4-fluorophenyl	
	$-CH_2CH_3$			2-methylphenyl	
	$-(CH_2)_2CH_3$			3-methylphenyl	
	$-(CH_2)_3CH_3$			4-methylphenyl	
	$-(CH_2)_4CH_3$			2-furyl	
	$-(CH_2)_5CH_3$			3-furyl	
	$-(CH_2)_6CH_3$			2-pyridyl	
	$-(CH_2)_7CH_3$			3-pyridyl	
	$-(CH_2)_8CH_3$			4-pyridyl	
	$-(CH_2)_9CH_3$			2,3-dimethoxyphenyl	
	$-(CH_2)_5OH$			2,4-dimethoxyphenyl	
	$-(CH_2)_6OH$			2,5-dimethoxyphenyl	
	$-(CH_2)_7OH$			2,6-dimethoxyphenyl	
	$-(CH_2)_8OH$			3,4-dimethoxyphenyl	
	$-(CH_2)_9OH$			3,5-dimethoxyphenyl	
	phenyl			2,3-dichlorophenyl	
	2-methoxyphenyl			2,4-dichlorophenyl	
	3-methoxyphenyl			2,5-dichlorophenyl	
	4-methoxyphenyl			2,6-dichlorophenyl	
	2-chlorophenyl			3,4-dichlorophenyl	
	3-chlorophenyl			2,4-dinitrophenyl	
	4-chlorophenyl			3,4-methylenedioxyphenyl	

(continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	2,3-methylene-dioxyphenyl	Ph	CO	2,5-dimethoxybenzyl	Ph
	1-naphthyl			3,4-dimethoxybenzyl	
	2-naphthyl			3,5-dimethoxybenzyl	
	2,3,4-trimethoxy-phenyl			2,4-dichlorobenzyl	
	2,3,6-trimethoxy-phenyl			2,6-dichlorobenzyl	
	2,4,5-trimethoxy-phenyl			3,4-dichlorobenzyl	
	2,4,6-trimethoxy-phenyl			2,4-dinitrobenzyl	
	3,4,5-trimethoxy-phenyl			3,4-methylenedi-oxybenzyl	
	2,3,5-trichloro-phenyl			2,3-methylenedi-oxybenzyl	
	2,4,6-trichloro-phenyl			3,4,5-trimethoxy-benzyl	
	benzyl			2-phenylethyl	
	2-methoxybenzyl			2-(2-methoxyphenyl)-ethyl	
	3-methoxybenzyl			2-(3-methoxyphenyl)-ethyl	
	4-methoxybenzyl			2-(4-methoxyphenyl)-ethyl	
	2-chlorobenzyl			2-(2,3-dimethoxy-phenyl)ethyl	
	3-chlorobenzyl			2-(3,4-dimethoxy-phenyl)ethyl	
	4-chlorobenzyl				
	2-fluorobenzyl				
	3-fluorobenzyl			2-(2,3,4-trimethoxy-phenyl)ethyl	
	4-fluorobenzyl				
	2-methylbenzyl			2-(3,4,5-trimethoxy-phenyl)ethyl	
	3-methylbenzyl				
	4-methylbenzyl			2-(2-chlorophenyl)-ethyl	
	2-pyridylmethyl			2-(4-chlorophenyl)-ethyl	
	3-pyridylmethyl				

(continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	2-(3,4-dichloro-phenyl)ethyl	Ph	SO_2	$-(CH_2)_7CH_3$	Ph
	2-(3,4-methylene-dioxyphenyl)ethyl			-Ph	
	3-phenylpropyl			$-CH_2Ph$	
	3-(4-methoxy-phenyl)propyl				
	3-(3,4-dimethoxy-phenyl)propyl				
	3-(3,4-methylene-dioxyphenyl)propyl				
(CO)O	Ph				
	$-CH_2Ph$				
(CO)NH	$-(CH_2)_7CH_3$				
	-Ph				
	$-CH_2Ph$				

(Continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	cyclohexyl	4-chloro-phenyl	CO	2-fluorophenyl	4-chloro-phenyl
	cyclohexyl-methyl			3-fluorophenyl	
	$-CH_3$			4-fluorophenyl	
	$-CH_2CH_3$			2-methylphenyl	
	$-(CH_2)_2CH_3$			3-methylphenyl	
	$-(CH_2)_3CH_3$			4-methylphenyl	
	$-(CH_2)_4CH_3$			2-furyl	
	$-(CH_2)_5CH_3$			3-furyl	
	$-(CH_2)_6CH_3$			2-pyridyl	
	$-(CH_2)_7CH_3$			3-pyridyl	
	$-(CH_2)_8CH_3$			4-pyridyl	
	$-(CH_2)_9CH_3$			2,3-dimethoxy-phenyl	
	$-(CH_2)_5OH$			2,4-dimethoxy-phenyl	
	$-(CH_2)_6OH$			2,5-dimethoxy-phenyl	
	$-(CH_2)_7OH$			2,6-dimethoxy-phenyl	
	$-(CH_2)_8OH$			3,4-dimethoxy-phenyl	
	$-(CH_2)_9OH$			3,5-dimethoxy-phenyl	
	phenyl			2,3-dichloro-phenyl	
	2-methoxy-phenyl			2,4-dichloro-phenyl	
	3-methoxy-phenyl			2,5-dichloro-phenyl	
	4-methoxy-phenyl			2,6-dichloro-phenyl	
	2-chloro-phenyl			3,4-dichloro-phenyl	
	3-chloro-phenyl			2,4-dinitro-phenyl	
	4-chloro-phenyl			3,4-methylene-dioxyphenyl	

(continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	2,3-methylene-dioxyphenyl	4-chloro-phenyl	CO	2,5-dimethoxy-benzyl	4-chloro-phenyl
	1-naphthyl			3,4-dimethoxy-benzyl	
	2-naphthyl			3,5-dimethoxy-benzyl	
	2,3,4-trimethoxy-phenyl			2,4-dichloro-benzyl	
	2,3,6-trimethoxy-phenyl			2,6-dichloro-benzyl	
	2,4,5-trimethoxy-phenyl			3,4-dichloro-benzyl	
	2,4,6-trimethoxy-phenyl			2,4-dinitro-benzyl	
	3,4,5-trimethoxy-phenyl			3,4-methylene-dioxybenzyl	
	2,3,5-trichloro-phenyl			2,3-methylene-dioxybenzyl	
	2,4,6-trichloro-phenyl			3,4,5-trimethoxy-benzyl	
	benzyl			2-phenylethyl	
	2-methoxybenzyl			2-(2-methoxy-phenyl)ethyl	
	3-methoxybenzyl			2-(3-methoxy-phenyl)ethyl	
	4-methoxybenzyl			2-(4-methoxy-phenyl)ethyl	
	2-chlorobenzyl			2-(2,3-dimethoxy-phenyl)ethyl	
	3-chlorobenzyl			2-(3,4-dimethoxy-phenyl)ethyl	
	4-chlorobenzyl				
	2-fluorobenzyl				
	3-fluorobenzyl			2-(2,3,4-tri-methoxy-phenyl)ethyl	
	4-fluorobenzyl				
	2-methylbenzyl			2-(3,4,5-tri-methoxyphenyl)-ethyl	
	3-methylbenzyl				
	4-methylbenzyl			2-(2-chloro-phenyl)ethyl	
	2-pyridylmethyl			2-(4-chloro-phenyl)ethyl	
	3-pyridylmethyl				

(continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	2-(3,4-dichloro-phenyl)ethyl	4-chloro-phenyl	SO_2	$-(CH_2)_7CH_3$	4-chloro-phenyl
	2-(3,4-methylene-dioxyphenyl)ethyl			-Ph	
	3-phenylpropyl			$-CH_2Ph$	
	3-(4-methoxy-phenyl)propyl				
	3-(3,4-dimethoxy-phenyl)propyl				
	3-(3,4-methylene-dioxyphenyl)-propyl				
(CO)O	Ph				
	$-CH_2Ph$				
(CO)NH	$-(CH_2)_7CH_3$				
	-Ph				
	$-CH_2Ph$				

(Continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	cyclohexyl	4-methoxyphenyl	CO	2-fluorophenyl	4-methoxyphenyl
	cyclohexylmethyl			3-fluorophenyl	
	$-CH_3$			4-fluorophenyl	
	$-CH_2CH_3$			2-methylphenyl	
	$-(CH_2)_2CH_3$			3-methylphenyl	
	$-(CH_2)_3CH_3$			4-methylphenyl	
	$-(CH_2)_4CH_3$			2-furyl	
	$-(CH_2)_5CH_3$			3-furyl	
	$-(CH_2)_6CH_3$			2-pyridyl	
	$-(CH_2)_7CH_3$			3-pyridyl	
	$-(CH_2)_8CH_3$			4-pyridyl	
	$-(CH_2)_9CH_3$			2,3-dimethoxyphenyl	
	$-(CH_2)_5OH$			2,4-dimethoxyphenyl	
	$-(CH_2)_6OH$			2,5-dimethoxyphenyl	
	$-(CH_2)_7OH$			2,6-dimethoxyphenyl	
	$-(CH_2)_8OH$			3,4-dimethoxyphenyl	
	$-(CH_2)_9OH$			3,5-dimethoxyphenyl	
	phenyl			2,3-dichlorophenyl	
	2-methoxyphenyl			2,4-dichlorophenyl	
	3-methoxyphenyl			2,5-dichlorophenyl	
	4-methoxyphenyl			2,6-dichlorophenyl	
	2-chlorophenyl			3,4-dichlorophenyl	
	3-chlorophenyl			2,4-dinitrophenyl	
	4-chlorophenyl			3,4-methylenedioxyphenyl	

(continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	2,3-methylene-dioxyphenyl	4-meth-oxy-phenyl	CO	2,5-dimethoxy-benzyl	4-meth-oxy-phenyl
	1-naphthyl			3,4-dimethoxy-benzyl	
	2-naphthyl			3,5-dimethoxy-benzyl	
	2,3,4-trimethoxy-phenyl			2,4-dichloro-benzyl	
	2,3,6-trimethoxy-phenyl			2,6-dichloro-benzyl	
	2,4,5-trimethoxy-phenyl			3,4-dichloro-benzyl	
	2,4,6-trimethoxy-phenyl			2,4-dinitro-benzyl	
	3,4,5-trimethoxy-phenyl			3,4-methylene-dioxybenzyl	
	2,3,5-trichloro-phenyl			2,3-methylene-dioxybenzyl	
	2,4,6-trichloro-phenyl			3,4,5-trimethoxy-benzyl	
	benzyl			2-phenylethyl	
	2-methoxybenzyl			2-(2-methoxy-phenyl)ethyl	
	3-methoxybenzyl			2-(3-methoxy-phenyl)ethyl	
	4-methoxybenzyl			2-(4-methoxy-phenyl)ethyl	
	2-chlorobenzyl			2-(2,3-dimethoxy-phenyl)ethyl	
	3-chlorobenzyl			2-(3,4-dimethoxy-phenyl)ethyl	
	4-chlorobenzyl				
	2-fluorobenzyl				
	3-fluorobenzyl			2-(2,3,4-trimethoxy-phenyl)ethyl	
	4-fluorobenzyl				
	2-methylbenzyl			2-(3,4,5-trimethoxy-phenyl)ethyl	
	3-methylbenzyl				
	4-methylbenzyl			2-(2-chloro-phenyl)ethyl	
	2-pyridylmethyl			2-(4-chlorop-henyl)ethyl	
	3-pyridylmethyl				

(continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	2-(3,4-dichloro-phenyl)ethyl	4-meth-oxy-phenyl	SO_2	$-(CH_2)_7CH_3$	4-meth-oxy-phenyl
	2-(3,4-methylene-dioxyphenyl)ethyl			-Ph	
	3-phenylpropyl			$-CH_2Ph$	
	3-(4-methoxy-phenyl)propyl				
	3-(3,4-dimethoxy-phenyl)propyl				
	3-(3,4-methylene-dioxyphenyl)propyl				
(CO)O	Ph				
	$-CH_2Ph$				
(CO)NH	$-(CH_2)_7CH_3$				
	-Ph				
	$-CH_2Ph$				

(Continued)

X^2	R^2	R^3	X^2	R^2	R^3
CO	cyclohexyl	4-meth-oxy-benzyl	CO	2-fluorophenyl	4-meth-oxy-benzyl
	cyclohexylmethyl			3-fluorophenyl	
	$-CH_3$			4-fluorophenyl	
	$-CH_2CH_3$			2-methylphenyl	
	$-(CH_2)_2CH_3$			3-methylphenyl	
	$-(CH_2)_3CH_3$			4-methylphenyl	
	$-(CH_2)_4CH_3$			2-furyl	
	$-(CH_2)_5CH_3$			3-furyl	
	$-(CH_2)_6CH_3$			2-pyridyl	
	$-(CH_2)_7CH_3$			3-pyridyl	
	$-(CH_2)_8CH_3$			4-pyridyl	
	$-(CH_2)_9CH_3$			2,3-dimethoxyphenyl	
	$-(CH_2)_5OH$			2,4-dimethoxyphenyl	
	$-(CH_2)_6OH$			2,5-dimethoxyphenyl	
	$-(CH_2)_7OH$			2,6-dimethoxyphenyl	
	$-(CH_2)_8OH$			3,4-dimethoxyphenyl	
	$-(CH_2)_9OH$			3,5-dimethoxyphenyl	
	phenyl			2,3-dichlorophenyl	
	2-methoxyphenyl			2,4-dichlorophenyl	
	3-methoxyphenyl			2,5-dichlorophenyl	
	4-methoxyphenyl			2,6-dichlorophenyl	
	2-chlorophenyl			3,4-dichlorophenyl	
	3-chlorophenyl			2,4-dinitrophenyl	
	4-chlorophenyl			3,4-methylene-dioxyphenyl	

(continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	2,3-methylene-dioxyphenyl	4-meth-oxy-benzyl	CO	2,5-dimethoxy-benzyl	4-meth-oxy-benzyl
	1-naphthyl			3,4-dimethoxy-benzyl	
	2-naphthyl			3,5-dimethoxy-benzyl	
	2,3,4-trimethoxy-phenyl			2,4-dichloro-benzyl	
	2,3,6-trimethoxy-phenyl			2,6-dichloro-benzyl	
	2,4,5-trimethoxy-phenyl			3,4-dichloro-benzyl	
	2,4,6-trimethoxy-phenyl			2,4-dinitrobenzyl	
	3,4,5-trimethoxy-phenyl			3,4-methylene-dioxybenzyl	
	2,3,5-trichloro-phenyl			2,3-methylene-dioxybenzyl	
	2,4,6-trichloro-phenyl			3,4,5-trimeth-oxybenzyl	
	benzyl			2-phenylethyl	
	2-methoxybenzyl			2-(2-methoxy-phenyl)ethyl	
	3-methoxybenzyl			2-(3-methoxy-phenyl)ethyl	
	4-methoxybenzyl			2-(4-methoxy-phenyl)ethyl	
	2-chlorobenzyl			2-(2,3-dimethoxy-phenyl)ethyl	
	3-chlorobenzyl			2-(3,4-dimethoxy-phenyl)ethyl	
	4-chlorobenzyl				
	2-fluorobenzyl				
	3-fluorobenzyl			2-(2,3,4-trimeth-oxyphenyl)ethyl	
	4-fluorobenzyl				
	2-methylbenzyl			2-(3,4,5-trimeth-oxyphenyl)ethyl	
	3-methylbenzyl				
	4-methylbenzyl			2-(2-chloro-phenyl)ethyl	
	2-pyridylmethyl			2-(4-chloro-phenyl)ethyl	
	3-pyridylmethyl				

(continued)

X^2	R^2	R^3	X^2	R^2	R^3
CO	2-(3,4-dichloro-phenyl)ethyl	4-meth-oxy-benzyl	SO_2	$-(CH_2)_7CH_3$	4-meth-oxy-benzyl
	2-(3,4-methylene-dioxyphenyl)ethyl			-Ph	
	3-phenylpropyl			$-CH_2Ph$	
	3-(4-methoxy-phenyl)propyl				
	3-(3,4-dimethoxy-phenyl)propyl				
	3-(3,4-methylene-dioxyphenyl)propyl				
(CO)O	Ph				
	$-CH_2Ph$				
(CO)NH	$-(CH_2)_7CH_3$				
	-Ph				
	$-CH_2Ph$				

(Continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	cyclohexyl	4-chloro-benzyl	CO	2-fluorophenyl	4-chloro-benzyl
	cyclohexyl-methyl			3-fluorophenyl	
	$-CH_3$			4-fluorophenyl	
	$-CH_2CH_3$			2-methylphenyl	
	$-(CH_2)_2CH_3$			3-methylphenyl	
	$-(CH_2)_3CH_3$			4-methylphenyl	
	$-(CH_2)_4CH_3$			2-furyl	
	$-(CH_2)_5CH_3$			3-furyl	
	$-(CH_2)_6CH_3$			2-pyridyl	
	$-(CH_2)_7CH_3$			3-pyridyl	
	$-(CH_2)_8CH_3$			4-pyridyl	
	$-(CH_2)_9CH_3$			2,3-dimethoxy-phenyl	
	$-(CH_2)_5OH$			2,4-dimethoxy-phenyl	
	$-(CH_2)_6OH$			2,5-dimethoxy-phenyl	
	$-(CH_2)_7OH$			2,6-dimethoxy-phenyl	
	$-(CH_2)_8OH$			3,4-dimethoxy-phenyl	
	$-(CH_2)_9OH$			3,5-dimethoxy-phenyl	
	phenyl			2,3-dichloro-phenyl	
	2-methoxyphenyl			2,4-dichloro-phenyl	
	3-methoxyphenyl			2,5-dichloro-phenyl	
	4-methoxyphenyl			2,6-dichloro-phenyl	
	2-chlorophenyl			3,4-dichloro-phenyl	
	3-chlorophenyl			2,4-dinitro-phenyl	
	4-chlorophenyl			3,4-methylene-dioxyphenyl	

(continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	2,3-methylene-dioxyphenyl	4-chloro-benzyl	CO	2,5-dimethoxy-benzyl	4-chloro-benzyl
	1-naphthyl			3,4-dimethoxy-benzyl	
	2-naphthyl			3,5-dimethoxy-benzyl	
	2,3,4-trimeth-oxyphenyl			2,4-dichloro-benzyl	
	2,3,6-trimeth-oxyphenyl			2,6-dichloro-benzyl	
	2,4,5-trimeth-oxyphenyl			3,4-dichloro-benzyl	
	2,4,6-trimeth-oxyphenyl			2,4-dinitrobenzyl	
	3,4,5-trimeth-oxyphenyl			3,4-methylene-dioxybenzyl	
	2,3,5-trichloro-phenyl			2,3-methylene-dioxybenzyl	
	2,4,6-trichloro-phenyl			3,4,5-trimethoxy-benzyl	
	benzyl			2-phenylethyl	
	2-methoxybenzyl			2-(2-methoxy-phenyl)ethyl	
	3-methoxybenzyl			2-(3-methoxy-phenyl)ethyl	
	4-methoxybenzyl			2-(4-methoxy-phenyl)ethyl	
	2-chlorobenzyl			2-(2,3-dimethoxy-phenyl)ethyl	
	3-chlorobenzyl			2-(3,4-dimethoxy-phenyl)ethyl	
	4-chlorobenzyl				
	2-fluorobenzyl				
	3-fluorobenzyl			2-(2,3,4-trimeth-oxyphenyl)ethyl	
	4-fluorobenzyl				
	2-methylbenzyl			2-(3,4,5-trimeth-oxyphenyl)ethyl	
	3-methylbenzyl				
	4-methylbenzyl			2-(2-chloro-phenyl)ethyl	
	2-pyridylmethyl			2-(4-chloro-phenyl)ethyl	
	3-pyridylmethyl				

(continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	2-(3,4-dichloro-phenyl)ethyl	4-chloro-benzyl	SO_2	$-(CH_2)_7CH_3$	4-chloro-benzyl
	2-(3,4-methylene-dioxyphenyl)ethyl			-Ph	
	3-phenylpropyl			$-CH_2Ph$	
	3-(4-methoxy-phenyl)propyl				
	3-(3,4-dimethoxy-phenyl)propyl				
	3-(3,4-methylene-dioxyphenyl)propyl				
(CO)O	Ph				
	$-CH_2Ph$				
(CO)NH	$-(CH_2)_7CH_3$				
	-Ph				
	$-CH_2Ph$				

(Continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	cyclohexyl	2-phenyl-ethyl	CO	2-fluorophenyl	2-phenyl-ethyl
	cyclohexyl-methyl			3-fluorophenyl	
	$-CH_3$			4-fluorophenyl	
	$-CH_2CH_3$			2-methylphenyl	
	$-(CH_2)_2CH_3$			3-methylphenyl	
	$-(CH_2)_3CH_3$			4-methylphenyl	
	$-(CH_2)_4CH_3$			2-furyl	
	$-(CH_2)_5CH_3$			3-furyl	
	$-(CH_2)_6CH_3$			2-pyridyl	
	$-(CH_2)_7CH_3$			3-pyridyl	
	$-(CH_2)_8CH_3$			4-pyridyl	
	$-(CH_2)_9CH_3$			2,3-dimethoxyphenyl	
	$-(CH_2)_5OH$			2,4-dimethoxyphenyl	
	$-(CH_2)_6OH$			2,5-dimethoxyphenyl	
	$-(CH_2)_7OH$			2,6-dimethoxyphenyl	
	$-(CH_2)_8OH$			3,4-dimethoxyphenyl	
	$-(CH_2)_9OH$			3,5-dimethoxyphenyl	
	phenyl			2,3-dichlorophenyl	
	2-methoxy-phenyl			2,4-dichlorophenyl	
	3-methoxy-phenyl			2,5-dichlorophenyl	
	4-methoxy-phenyl			2,6-dichlorophenyl	
	2-chloro-phenyl			3,4-dichlorophenyl	
	3-chloro-phenyl			2,4-dinitrophenyl	
	4-chloro-phenyl			3,4-methylene-dioxyphenyl	

(continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	2,3-methylene-dioxyphenyl	2-phenyl-ethyl	CO	2,5-dimethoxy-benzyl	2-phenyl-ethyl
	1-naphthyl			3,4-dimethoxy-benzyl	
	2-naphthyl			3,5-dimethoxy-benzyl	
	2,3,4-trimethoxy-phenyl			2,4-dichloro-benzyl	
	2,3,6-trimethoxy-phenyl			2,6-dichloro-benzyl	
	2,4,5-trimethoxy-phenyl			3,4-dichloro-benzyl	
	2,4,6-trimethoxy-phenyl			2,4-dinitro-benzyl	
	3,4,5-trimethoxy-phenyl			3,4-methylene-dioxybenzyl	
	2,3,5-trichloro-phenyl			2,3-methylene-dioxybenzyl	
	2,4,6-trichloro-phenyl			3,4,5-trimeth-oxybenzyl	
	benzyl			2-phenylethyl	
	2-methoxybenzyl			2-(2-methoxy-phenyl)ethyl	
	3-methoxybenzyl			2-(3-methoxy-phenyl)ethyl	
	4-methoxybenzyl			2-(4-methoxy-phenyl)ethyl	
	2-chlorobenzyl			2-(2,3-dimeth-oxyphenyl)ethyl	
	3-chlorobenzyl			2-(3,4-dimeth-oxyphenyl)ethyl	
	4-chlorobenzyl				
	2-fluorobenzyl				
	3-fluorobenzyl			2-(2,3,4-trimethoxy-phenyl)ethyl	
	4-fluorobenzyl				
	2-methylbenzyl			2-(3,4,5-tri-methoxyphenyl)-ethyl	
	3-methylbenzyl				
	4-methylbenzyl			2-(2-chloro-phenyl)ethyl	
	2-pyridylmethyl			2-(4-chloro-phenyl)ethyl	
	3-pyridylmethyl				

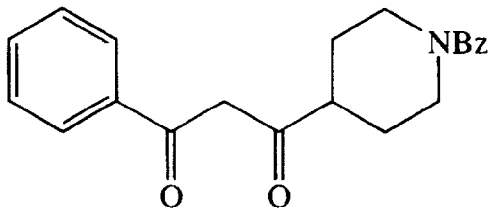
(continued)

X^2	R^1	R^3	X^2	R^1	R^3
CO	2-(3,4-dichloro-phenyl)ethyl	2-phenyl-ethyl	SO_2	$-(CH_2)_7CH_3$	2-phenyl-ethyl
				-Ph	
	2-(3,4-methylene-dioxyphenyl)-ethyl			$-CH_2Ph$	
	3-phenylpropyl		CO	3,4-methylene dioxy-phenyl	4-iodo-benzyl
	3-(4-methoxy-phenyl)propyl				4-fluoro-benzyl
	3-(3,4-dimethoxy-phenyl)propyl				4-methyl-thio-benzyl
					4-methyl-sulfinyl-benzyl
					4-methyl-sulfonyl-benzyl
	3-(3,4-methylene-dioxyphenyl)-propyl				4-amino-benzyl
					4-pyridyl-methyl
(CO)O	-Ph				
	$-CH_2Ph$				
(CO)NH	$-(CH_2)_7CH_3$				
	-Ph				
	$-CH_2Ph$				

Hereinafter the present invention will be described in more detail by referring to the following Examples but is not deemed to be limited thereto. In the chemical formulas illustrated hereinbelow, the symbols "Bz" and "Ac" are used to mean benzoyl and acetyl, respectively. Melting points are uncorrected.

Example 1 Synthesis of 2-amino-4-(1-benzoyl-4-piperidinyl)-6-phenylpyrimidine

(1) 1-Benzoyl-4-[1-(1,3-dioxo-3-phenylpropyl)]piperidine

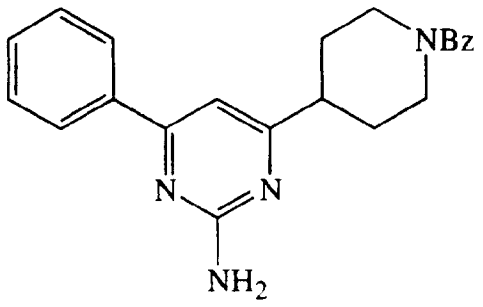


Ethyl 1-benzoylisonipecotate (30 g, 0.115 mol) and acetophenone (13.82 g, 0.115 mol) were dissolved in 320 ml of tetrahydrofuran (THF). To the solution was added sodium hydride (60% dispersion in mineral oil) (4.6 g, 0.115 mol). The mixture was heated at about 60°C for about 3.5 hours under a nitrogen atmosphere. The reaction mixture was then neutralized with 1 N hydrochloric acid and the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 8 : 2). Crystallization from diethyl ether gave the titled compound (11.86 g).

Melting point: 104-105°C

^{1}H-NMR ($CDCl_3$): δ 1.77 (4H, m), 2.62 (1H, m), 2.99 (2H, m), 3.88 (1H, m), 4.78 (1H, m), 6.21 (1H, s), 7.49 (8H, m), 7.88 (2H, dd, J=1.3, J=6.6), 16.21 (1H, s)

(2) 2-Amino-4-(1-benzoyl-4-piperidinyl)-6-phenylpyrimidine



A mixture of 1-benzoyl-4-[1-(1,3-dioxo-3-phenylpropyl)]piperidine (11 g, 0.033 mol), guanidine hydrochloride (6.3 g, 0.066 mol) and potassium carbonate (9.12 g, 0.066 mol) in pyridine (50 ml) was stirred at about 100°C for about 6 hours. Potassium carbonate (4.56 g, 0.033 mol) and guanidine hydrochloride (3.15 g, 0.033 mol) were further added to the reaction mixture and stirred for about 10 hours at the same temperature. Thereafter dichloromethane and water were added to the reaction mixture followed by extraction. The organic layer was dried over sodium sulfate, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1). Crystallization from isopropyl alcohol gave the titled

compound (8.60 g).

Melting point: 147-148°C

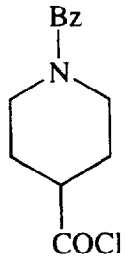
^{1}H-NMR ($CDCl_3$): δ 1.88 (4H, m), 2.77-3.44 (3H, m), 3.93 (1H, m), 4.89 (1H, m), 5.05 (2H, brs), 6.93 (1H, s), 7.45 (8H, m), 7.97 (2H, m)

The resulting free amine compound (600 mg) was dissolved in methanol and acidified with 1 N hydrogen chloride-diethyl ether solution. The solvent was then removed in vacuo. The residue was triturated with methanol-diethyl ether to give the hydrochloride (582 mg) of the titled compounds.

Melting point: 132-134°C

Example 2 Synthesis of 2-amino-4-(1-benzoyl-4-piperidinyl)-6-(4-methoxyphenylmethyl)pyrimidine

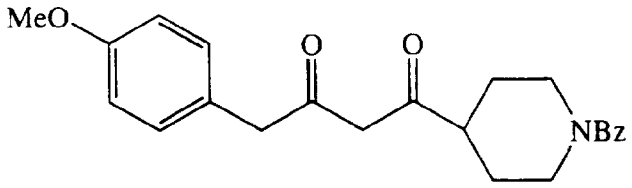
(1) 1-Benzoyl-4-piperidinecarbonyl chloride



A mixture of 1-benzoylisonipecotic acid (60 g, 0.257 mol) thionyl chloride (38 ml) and chloroform (360 ml) was refluxed for about 3 hours. Thereafter the reaction mixture was concentrated in vacuo. Toluene was added to the residue and the mixture was concentrated in vacuo to remove an excess of thionyl chloride. The

titled compound was obtained as a crude oil.

(2) 1-Benzoyl-4-{1-[4-(4-methoxyphenyl)-1,3-dioxobutyl]}piperidine



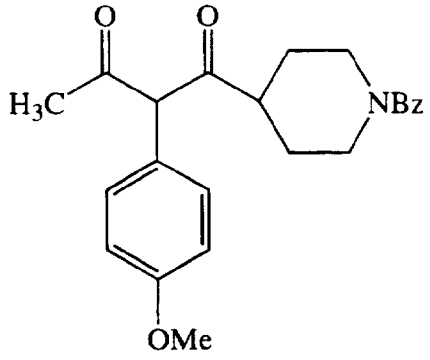
Diisopropylamine (72 ml, 0.514 mol) was dissolved in THF (510 ml). Under a nitrogen atmosphere n-butyl lithium-hexane solution (310 ml, 1.66 mmol/ml) was added dropwise to the solution over a period of about 1.5 hours at about 0°C. After stirring at the same temperature for about 30 minutes, the mixture was cooled to about -78°C and 4-methoxyphenylacetone (84.4 g, 1.03 mol) was added dropwise over a period of about 1.5 hour and stirred for about 30 minutes. A solution of 1-benzoyl-4-piperidinecarbonyl chloride of Example 2 (1) in THF (510 ml) was added dropwise to the mixture over a period of about 2 hours at the same temperature.

Thirty minutes later conc. hydrochloric acid was added to the reaction mixture. Ethyl acetate and water were then added to the mixture for extraction. The organic layer was washed with water and dried over magnesium sulfate, and then the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 6 : 4) to give

the titled compound (35.5 g) as an oil.

^{1}H-NMR ($CDCl_3$): δ 1.70 (4H, m), 2.38 (1H, m), 2.86 (2H, m), 3.65 (2H, s), 3.75 (1H, m), 3.82 (3H, s), 4.73 (1H, m), 5.43 (1H, s), 6.90 (1H, d, J=7.6), 6.97 (1H, d, J=7.6), 7.18 (1H, d, J=7.6), 7.28 (1H, d, J=7.6),7.40 (5H, m), 15.45 (1H, s)

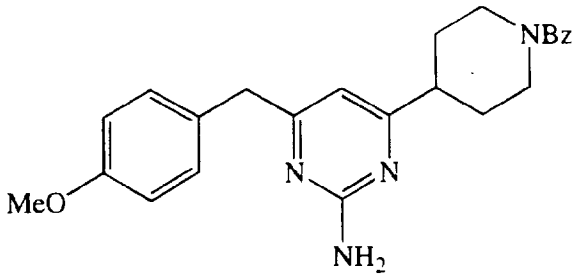
In this reaction 35.5 g of 1-benzoyl-4-{1-[2-(4-methoxyphenyl)-1,3-dioxobutyl]} piperidine was also obtained as a crystal.



Melting point: 134-137°C

^{1}HNMR ($CDCl_3$): δ 1.56-1.72 (4H, m), 1.88 (3H, s), 2.42 (1H, m), 2.65 (2H, m), 3.70 (1H, m), 3.85 (3H, s), 4.67 (1H, m), 6.92 (2H, d, J=7.9), 7.06 (2H, d, J=7.9), 7.37 (5H, m), 16.86 (1H, s)

(3) 2-Amino-4-(1-benzoyl-4-piperidinyl)-6-(4-methoxyphenylmethyl)pyrimidine



By a procedure similar to that described in Example 1(2) and crystallization from ethanol, the titled compound (15.3 g) was prepared from 1-benzoyl-4-{1-[4-(4-methoxyphenyl)-1,3-dioxobutyl]}piperidine (33 g, 0.084 mol).

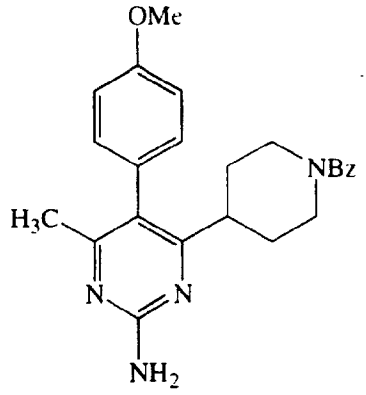
Melting point: 170-171°C

^{1}H-NMR ($CDCl_3$): δ 1.75 (4H, m), 2.65 (1H, m), 2.93(2H, m), 3.80 (3H, s), 3.83 (2H, s), 3.85(1H, m), 4.80 (1H, m), 4.94 (2H, brs), 6.26 (1H, s), 6.86 (2H, d, J=8.6), 7.16 (2H, d, J=8.6), 7.40 (5H, m)

The titled compound (250 mg) in methanol was acidified with 1 N hydrogen chloride-diethyl ether solution. The solvent was then removed in vacuo. The residue was triturated with tetrahydrofuran-diethyl ether to give the hydrochloride (270mg) of the titled compound.

Melting point: 169-170°C

Example 3 Synthesis of 2-amino-4-(1-benzoyl-4-piperidinyl)-5-(4-methoxyphenyl)-6-methylpyrimidine



By a procedure similar to that described in Example 1(2) and crystallization from ethanol, the titled compound (2.14 g) was prepared from 1-benzoyl-4-{1-[2-(4-methoxyphenyl)-1,3-dioxobutyl]}piperidine(30 g, 0.076 mol).

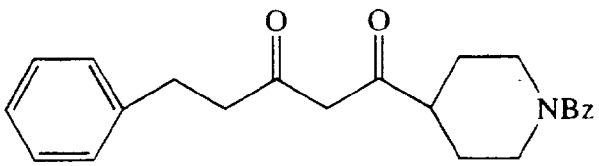
Melting point: 226-227°C

^{1}H-NMR ($CDCl_3$): δ 1.63-1.98 (4H, m), 2.52-2.81 (3H, m), 2.08 (3H, s), 3.78 (1H, m), 3.87(3H, s), 4.71 (1H, m), 4.90 (2H, brs), 7.00 (4H, m), 7.39 (5H, m).

The titled compound (50 mg) in methanol was acidified with hydrogen chloride-diethyl ether solution. The solvent was then removed in vacuo. The residue was triturated with tetrahydrofuran-diethyl ether to give the hydrochloride (50 mg) of the titled compound.

Example 4 Synthesis of 2-amino-4-(1-benzoyl-4-piperidinyl)-6-(2-phenylethyl)pyrimidine

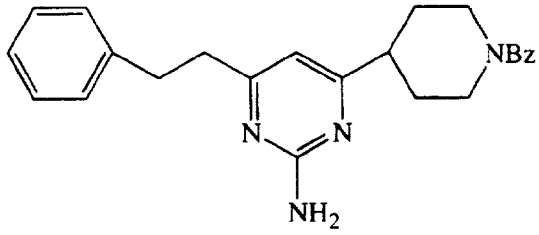
(1) 1-Benzoyl-4-[1-(1,3-dioxo-5-phenylpentyl)]piperidine



By a procedure similar to that described in Example 2 (1) and (2), the titled compound (29.9 g) as an oil was prepared from 1-benzoylisonipecotic acid (50 g, 0.214 mol) and benzylacetone (38.06g, 0.257 mol).

^{1}H-NMR ($CDCl_3$): δ 1.63 (3H, m), 2.43 (1H, m), 2.63(2H, t, J=7.3), 2.91 (5H, m), 3.83 (1H, m), 4.71 (1H, m), 5.46 (1H, s), 7.30 (10H, m), 15.48 (1H, brs)

(2) 2-Amino-4-(1-benzoyl-4-piperidinyl)-6-(2-phenylethyl)pyrimidine



By a procedure similar to that described in Example 1(2) and crystallization from ethanol, the titled compound (23.8 g) was prepared from 1-benzoyl-4-[1-(1,3-dioxo-5-phenyl-pentyl)]piperidine (29 g, 0.080 mol).
Melting point: 104-106°C

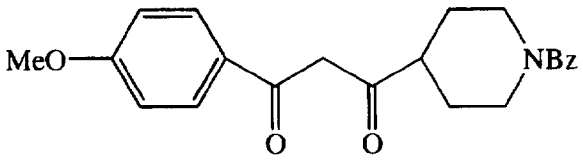
^{1}H-NMR ($CDCl_3$): δ 1.78 (4H, m), 2.67 (1H, m), 2.84-3.01 (6H, m), 3.85 (1H, m), 4.80 (1H, m), 4.93 (2H, brs), 6.27 (1H, s), 7.17-7.42 (10H, m)

The titled compound (400 mg) in methanol was acidified with 1 N hydrogen chloride-diethyl ether solution. The solvent was then removed in vacuo. The residue was triturated with tetrahydrofuran-diethyl ether to give of the hydrochloride (437 mg) of the titled compound.

Melting point: 216-217°C

Example 5 Synthesis of 2-amino-4-(1-benzoyl-4-piperidinyl)-6-(4-methoxyphenyl)pyrimidine

(1) 1-Benzoyl-4-{1-[3-(4-methoxyphenyl)-1,3-dioxo-propyl]}piperidine



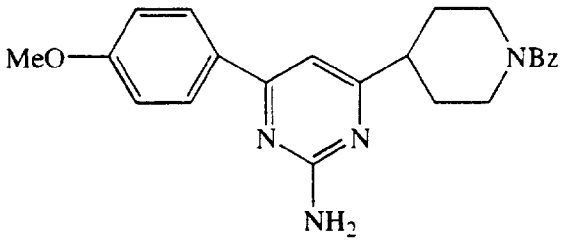
By a procedure similar to that described in Example 2(1) and (2) and crystallization from diethyl ether, the titled compound (11.67 g) was prepared from 1-benzoylisonipecotic acid (15.16 g, 0.065 mol) and 4'-methoxyacetophenone (19.52 g, 0.13 mol).

Melting point: 226-227°C

1H-NMR ($CDCl_3$): δ 1.76 (4H, m), 2.58 (1H, m), 2.91 (2H, m), 3.88 (4H, m), 4.78 (1H, m), 6.14 (1H, s), 6.95 (2H, d, J=8.6), 7.42 (5H, m), 7.87 (2H, d, J=8.6), 16.38 (1H, s)

(2) 2-Amino-4-(1-benzoyl-4-piperidinyl)-6-(4-

methoxyphenyl)pyrimidine



By a procedure similar to that described in Example 1(2) and crystallization from ethanol, the titled compound (7.81 g) was prepared from 1-benzoyl-4-{1-[3-(4-methoxyphenyl)-1,3-dioxopropyl]}piperidine (10 g, 0.027 mol).

Melting point: 165-166°C

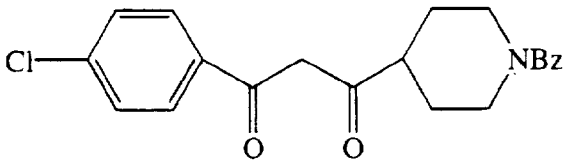
^{1}H-NMR ($CDCl_3$): δ 1.88 (4H, m), 2.79 (1H, m), 3.00(2H, m), 3.87 (4H, m), 4.90 (1H, m), 5.02 (2H, s), 6.87 (1H, s), 6.98 (2H, d, J=8.6), 7.43 (5H, m), 7.96(2H, d, J=8.6).

The titled compound (110 mg) in chloroform was acidified with 1 N-hydrogen chloride-diethyl ether solution. The solvent was removed in vacuo. The residue was triturated with chloroform-diethyl ether to give the hydrochloride (100 mg) of the titled compound.

Melting point: 249-253°C

Example 6 Synthesis of 2-amino-4-(1-benzoyl-4-piperidinyl)-6-(4-chlorophenyl)pyrimidine

(1) 1-Benzoyl-4-{1-[3-(4-chlorophenyl)-1,3-dioxopropyl]}piperidine

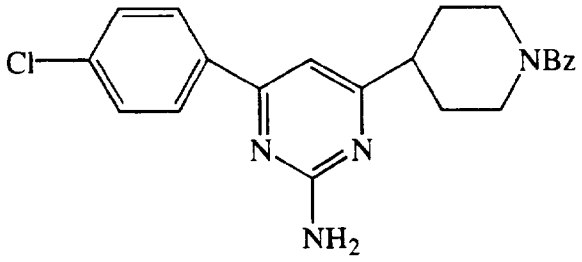


By a procedure similar to that described in Example 2(1) and (2) and crystallization from diethyl ether, the titled compound (11.92 g) was prepared from 1-benzoylisonipecotic acid (15.16 g, 0.065 mol) and 4'-chloroacetophenone (20.98 g, 0.13 mol).

Melting point: 129-130°C

^{1}H-NMR ($CDCl_3$): δ 1.77 (4H, m), 2.62 (1H, m), 2.95 (2H, m), 3.88 (1H, m), 4.78 (1H, m), 6.16 (1H, s), 7.44 (7H, m), 7.83(2H, d, J=8.6), 16.16 (1H, s).

(2) 2-Amino-4-(1-benzoyl-4-piperidinyl)-6-(4-chlorophenyl)pyrimidine



By a procedure similar to that described in Example 1(2) and crystallization from isopropanol, the titled compound (7.25 g) was prepared from 1-benzoyl-4-{1-[3-(4-chlorophenyl)-1,3-dioxopropyl]}piperidine(10 g, 0.027mol).

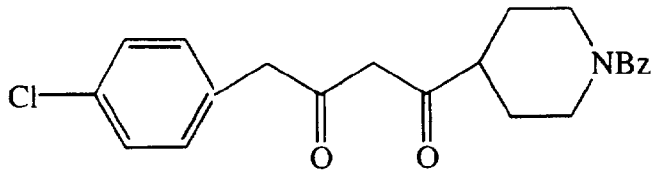
Melting point: 210-211°C

^{1}H-NMR ($CDCl_3$): δ 1.87 (4H, m), 2.81 (1H, m),3.00 (2H, m), 3.90 (1H, m), 4.87 (1H, m), 5.08 (2H, s), 6.89 (1H, s),7.44 (7H, m), 7.94 (2H, d, J=8.6).

The titled compound (110 mg) in chloroform was acidified with 1 N-hydrogen chloride-diethyl ether solution. The solvent was removed in vacuo. The residue was triturated with chloroform-diethyl ether to give the hydrochloride (85 mg) of the titled compound.
Melting point: 238-239°C

Example 7 Synthesis of 2-amino-4-(1-benzoyl-4-piperidinyl)-6-(4-chlorophenylmelthyl)pyrimidine

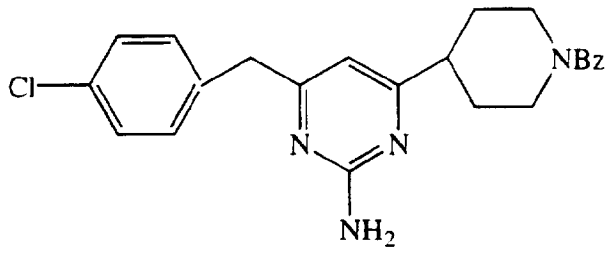
(1) 1-Benzoyl-4-{1-[4-(4-chlorophenyl)-1,3-dioxobutyl]}piperidine



By a procedure similar to that described in Example 2(1) and (2), the title compound (9.86 g) was prepared from 1-benzoylisonipecotic acid (27.64 g, 0.119 mol) and 4'-chlorophenylacetone (40 g, 0.237 mol).

^{1}H-NMR ($CDCl_3$): δ 1.55-1.90 (4H, m), 2.41 (1H, m), 2.92 (2H, m), 3.58 (2H, s), 3.78(1H, m), 4.71 (1H, m), 5.44 (1H, s), 7.17(2H, d, J=8.6), 7.27 (2H, d, J=8.6),7.40 (5H, m), 15.37 (1H, s).

(2) 2-Amino-4-(1-benzoyl-4-piperidinyl)-6-(4-chlorophenylmethyl)pyrimidine



By a procedure similar to that described in Example 1(2) and crystallization from methanol, the titled compound (5.54 g) was prepared from 1-benzoyl-4-{1-[4-(4-chlorophenyl)-1,3-dioxobutyl]}piperidine (9.0 g, 0.023mol).

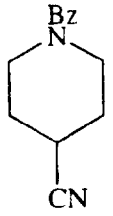
^{1}H-NMR ($CDCl_3$): δ 1.76 (4H, m), 2.66 (1H, m), 2.86(2H, m), 3.85 (2H, s), 3.90 (1H, m), 4.80 (1H, m), 4.99 (2H, brs), 6.26(1H, s), 7.18 (2H, d, J=8.3), 7.28(2H, d, J=8.3), 7.40 (5H, m).

The titled compound (180 mg) in chloroform was acidified with 1 N-hydrogen chloride-diethyl ether solution. The solvent was removed in vacuo. The residue was triturated with chloroform-diethyl ether to give the hydrochloride (194 mg) of the titled compound.
Melting point: 148-150°C

Example 8 Synthesis of 2-amino-4-(1-benzoyl-4-piperidinyl)quinazoline

(1) 1-Benzoyl-4-cyanopiperidine

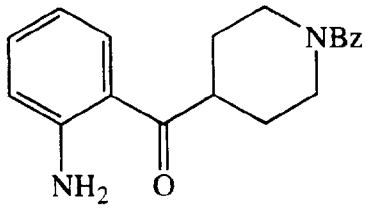
(2)



By a procedure similar to that described later in Reference Example 1 and crystallization from isopropanol, the titled compound (73.5 g) was prepared from 4-cyanopiperidine(40 g, 0.363mol).

^{1}H-NMR ($CDCl_3$): δ 1.91 (4H, m), 2.93 (1H, m), 3.20-4.10 (4H, m), 7.40 (5H, m)

(2) 1-Benzoyl-4-(2-aminobenzoyl)piperidine



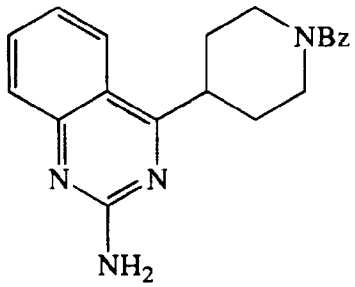
To an ice cold solution of boron trichloride (26.3 ml, 0.303 mol) in 300 ml of 1,2-dichloroethane was added dropwise aniline (28.21 g, 0.303 mol) over a period of about 15 minutes under a nitrogen atmosphere. Then to the solution was added portionwise 1-benzoyl-4-cyanopiperidine (50 g, 0.233 mol) and aluminum chloride (40.39 g, 0.303 mol) successively. After stirring at room temperature for about 15 minutes, the mixture was refluxed for about 14 hours. After 1 N hydrochloric acid aqueous solution was added to the reaction mixture at

about ice cooling temperature, the mixture was refluxed for about an hour. To the reaction mixture 3 N sodium hydroxide was added to make basic. The resulting slurry was filtered over Celite. The filtrate was extracted with dichloromethane. The organic layer was dried over sodium sulfate, and the solvent was removed in vacuo. The residue was crystallized from ethanol to give 51.4 g of the titled compound.

Melting point: 138-138.5°C

^{1}H-NMR ($CDCl_3$): δ 1.64-1.90 (4H, m), 3.07 (2H,m),3.56 (1H, m), 3.92 (1H, m), 4.75 (1H, m), 6.31 (2H, brs), 6.64 (2H, t, J=7.6), 7.25-7.41 (6H, m), 7.74 (1H, d, J=7.6)

(3) 2-Amino-4-(1-benzoyl-4-piperidinyl)quinazoline



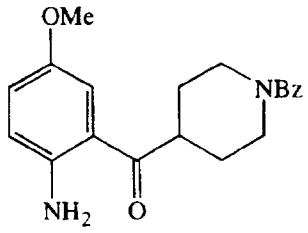
The titled compound was prepared by warming a mixture of 1-benzoyl-4-(2-aminobenzoyl)piperidine hydrochloride (17 g, 0.049 mol) and cyanamide (4.12 g, 0.098 mol). At about 50°C, vigorous exothermic reaction occurred. After the reaction was finished, the reaction mixture was cooled, water was added to the reaction mixture, and then added sodium hydrogencarbonate to make the mixture basic. The mixture was then extracted with

dichloromethane. The organic layer was washed with aqueous solution of saturated sodium chloride , and then dried over sodium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to give the titled compound (15.9 g) as a foam.

^{1}H-NMR ($CDCl_3$): δ 1.80-2.10 (4H, m), 3.20 (2H, m), 3.70 (1H, m), 3.96 (1H, m), 4.89 (1H, m), 5.13 (2H, brs), 7.26-7.71 (9H, m)

Example 9 Synthesis of 2-amino-4-(1-benzoyl-4-piperidinyl)-6-methoxyquinazoline

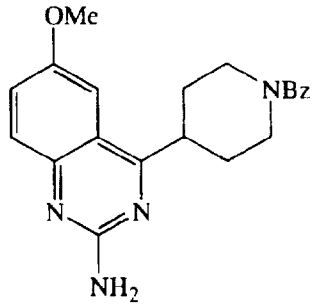
(1) 1-Benzoyl-4-(2-amino-5-methoxybenzoyl)piperidine



By a procedure similar to that described in Example 8(2), the title compound (8.12 g) was prepared from 4-methoxyaniline (10.26 g, 0.083 mol) and 1-benzoyl-4-cyanopiperidine (21.53 g, 0.10 mol).

^{1}H-NMR ($CDCl_3$): δ 1.60-1.95 (4H, m), 2.95 (2H, m), 3.41 (1H, m), 3.69 (3H, s), 3.75(1H, m), 4.65 (1H, m), 5.95 (2H, brs), 6.57 (1H, d, J=8.9), 6.90 (1H, dd, J=8.9, J=3.0), 7.12 (1H, d, J=3.0), 7.30 (5H, m).

(2) 2-Amino-4-(1-benzoyl-4-piperidinyl)-6-methoxyquinazoline



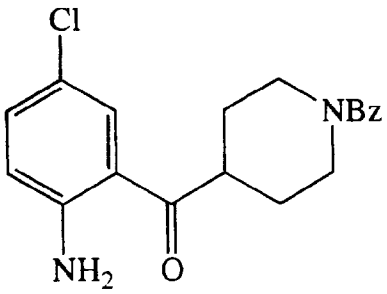
By a procedure similar to that described in Example 8(3), the titled compound (4.15 g) was prepared from 1-benzoyl-4-(2-amino-5-methoxybenzoyl)piperidine hydrochloride (4.51 g, 0.012 mol).

Melting point: 172-173°C

^{1}H-NMR ($CDCl_3$): δ 1.88-2.08 (4H, m), 3.07 (2H, m), 3.61 (1H, m), 3.92 (3H, s), 3.95 (1H, m), 5.00 (3H, m), 7.19 (1H, d, J=2.4), 7.27-7.50 (6H, m), 7.56 (1H, d, J=9.2).

Example 10 Synthesis of 2-amino-4-(1-benzoyl-4-piperidinyl)-6-chloroquinazoline

(1) 1-Benzoyl-4-(2-amino-5-chlorobenzoyl)piperidine

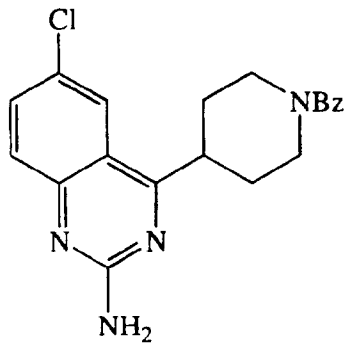


By a procedure similar to that described in Example 8(2), the titled compound (808 mg) was prepared

from 4-chloroaniline (2.18 g, 0.017 mol) and 1-benzoyl-4-cyanopiperidine (4.03 g, 0.018 mol).

^{1}H-NMR ($CDCl_3$): δ 1.76-1.99 (4H, m), 2.98 (2H, m), 3.46 (1H, m), 3.83 (1H, m), 4.72 (1H, m), 6.40 (2H, brs), 6.61 (1H, d, J=8.9), 7.17 (1H, dd, J=8.9, J=2.2), 7.40 (5H, m), 7.64 (1H, d, J=2.2).

(2) 2-Amino-4-(1-benzoyl-4-piperidinyl)-6-chloroquinazoline



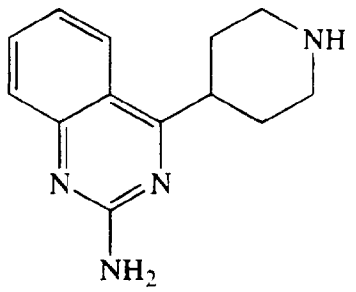
By a procedure similar to that described in Example 8(3), the titled compound (477 mg) was prepared from 1-benzoyl-4-(2-amino-5-methoxybenzoyl)-piperidine hydrochloride (800 mg, 2.1 mmol).

Melting point: 155-158°C

^{1}H-NMR ($CDCl_3$): δ 1.80-2.12 (4H, m), 3.14 (2H, m), 3.61 (1H, m), 3.96 (1H, m), 4.91 (1H, m), 5.15 (2H, s), 7.42-7.65 (7H, m), 7.90 (1H, d, J=2.0).

Example 11 Synthesis of 4-(1-acetyl-4-piperidinyl)-2-aminoquinazoline

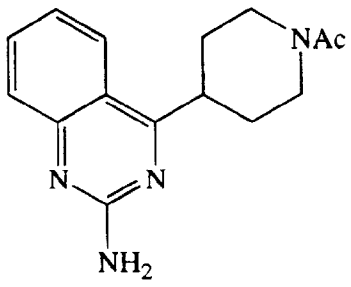
(1) 2-Amino-4-(4-piperidinyl)quinazoline



A mixture of 2-amino-4-(1-benzoyl-4-piperidinyl)quinazoline (24 g, 0.072 mol) obtained in Example 8 (3), ethanol (250 ml) and 6 N sodium hydroxide aqueous solution (250 ml) was refluxed for about 7 hours under a nitrogen atmosphere. Thereafter ethanol was removed from the reaction mixture in vacuo. The residue was extracted with dichloromethane. The organic layer was washed with saturated sodium chloride aqueous solution, and then dried over magnesium sulfate and evaporated in vacuo. The residue was crystallized from isopropyl alcohol to give 13.0 g of the titled compound.
Melting point: 184-186°C

^{1}H-NMR ($CDCl_3$): δ 1.78-1.96 (5H, m), 2.85 (2H, ddd, J=3.3, J=11.9, J=11.9), 3.26 (2H, dd, J=3.3, J=11.9), 3.56 (1H, m), 5.14 (2H, brs), 7.27 (1H, dd, J=8.3, J=5.9), 7.57-7.69 (2H, m), 7.96 (1H, d, J=8.3)

(2) 4-(1-Acetyl-4-piperidinyl)-2-aminoquinazoline



To an ice cold solution of 2-amino-4-(4-piperidyl)quinazoline (500 mg, 2.19 mmols) and triethylamine (233 mg, 2.3 mmol) in N,N-dimethylformamide (10 ml) was added dropwise acetic anhydride (0.22 ml, 2.30 mmol) under a nitrogen atmosphere. The reaction mixture was stirred for about 3 hours and was evaporated. The residue was partitioned between dichloromethane and saturated sodium hydrogencarbonate aqueous solution. The organic layer was washed with water and then dried over sodium sulfate and evaporated in vacuo. The residue was crystallized from ethanol. Recrystallization from methanol gave the titled compound(452 mg).

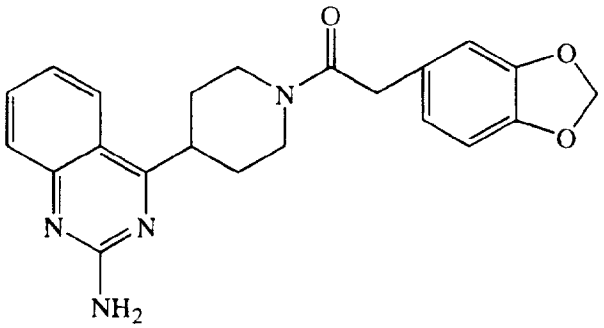
Melting point: 239-240°C

^{1}H-NMR ($CDCl_3$): δ 1.96 (4H, m), 2.16 (3H, s), 2.77 (1H, m), 3.30 (1H, m), 3.66 (1H, m), 4.00 (1H, m), 4.79 (1H, m), 5.12 (2H, brs), 7.28 (1H, m), 7.65 (2H, m), 7.94 (1H, d, J=7.9)

The titled compound (290 mg) in methanol was acidified with 1 N hydrogen chloride-diethyl ether solution. The solvent was then removed in vacuo. The residue was crystallized from isopropyl alcohol to give the hydrochloride (324 mg) of the titled compound.

Melting point: 275°C (decomposed)

Example 12 Synthesis of 2-amino-4-[1-(3,4-methylenedioxyphenylacetyl)-4-piperidinyl]quinazoline



To a suspension of 3,4-methylenedioxyphenylacetic acid (569 mg, 3.16 mmol) in chloroform (6 ml) was added thionyl chloride (1.2 ml). The mixture was refluxed for about 3 hours, and was evaporated. Toluene was added to the residue and the mixture was evaporated to remove the excess of thionyl chloride. To the residue was added dichloromethane (3 ml) to give a dichloromethane solution of 3,4-methylenedioxyphenylacetyl chloride. To an ice cold mixture of 2-amino-4-(4-piperidinyl)quinazoline (600 mg, 2.63 mmol) and triethylamine (319 mg, 3.16 mmol) in dichloromethane (16 ml) was added dropwise the solution of 3,4-methylenedioxyphenylacetyl chloride prepared above under a nitrogen atmosphere. The mixture was stirred for about two hours and to the reaction mixture was added dichloromethane and saturated sodium hydrogencarbonate aqueous solution followed by extraction. The organic layer was washed with water, and then dried over sodium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (dichloromethane : methanol = 30 : 1). Crystallization

from methanol gave the titled compound (617 mg).

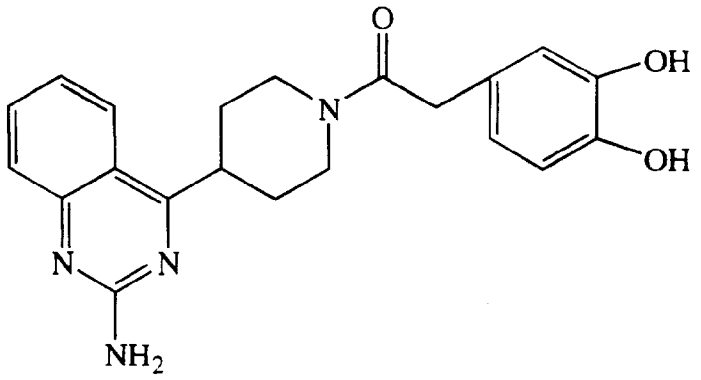
Melting point: 167-168°C.

^{1}H-NMR ($CDCl_3$): δ 1.89 (4H, m), 2.83 (1H, m), 3.21(1H, m), 3.59 (1H, m), 3.70 (2H, s), 4.05 (1H, m), 4.79 (1H, m), 5.10 (2H, brs), 5.95 (2H, s), 6.75 (3H, m), 7.27 (1H, m), 7.59 (1H, d, J=7.6), 7.67 (1H, m), 7.90 (1H, d, J=7.6)

The titled compound (260 mg) in methanol was acidified with 1 N hydrogen chloride-diethyl ether solution. The solvent was then removed in vacuo. Crystallization from ethanol gave the hydrochloride (280 mg) of the titled compound.

Melting point: 157-160°C

Example 13 Synthesis of 2-amino-4-[1-(3,4-dihydroxy-phenylacetyl)-4-piperidinyl]quinazoline



To an ice-cold solution of 2-amino-4-(4-piperidinyl)quinazoline (600 mg, 2.63 mmol) obtained in example 11(1), 3,4-dihydroxyphenylacetic acid (530 mg, 3.16 mmol) and 4-dimethylaminopyridine (386 mg, 3.16

mmol) in dimethylformamide (20 ml) was added 1-ethyl-3-(N,N'-dimethylaminopropyl)carbodiimide hydrochloride (605 mg, 3.16 mmol) under a nitrogen atmosphere. The mixture was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was crystallized from methanol to give the titled compound (599 mg).

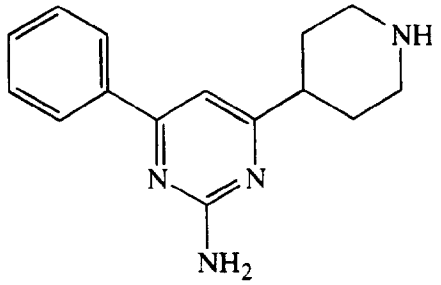
Melting point: 250-253°C

^{1}H-NMR (DMSO-d_6): δ 1.72 (4H, m), 2.79 (1H, m), 3.17-3.58 (3H, m), 3.76 (1H, m), 4.06 (1H, m), 4.54 (1H, m), 6.51 (1H, d, J=7.9), 6.66 (4H, m), 7.20 (1H, dd, J=6.9, J=7.3), 7.41 (1H, d, J=7.3), 7.64 (1H, dd, J=6.9, J=7.6), 8.07 (1H, d, J=7.6), 8.79 (2H, brs).

The titled compound (200 mg) in methanol was acidified with 1 N-hydrogen chloride-diethylether solution. The solvent was removed in vacuo. Crystallization from ethanol gave the hydrochloride (150 mg) of the titled compound.

Examples 14 to 267

(1) 2-Amino-4-phenyl-6-(4-piperidinyl)pyrimidine



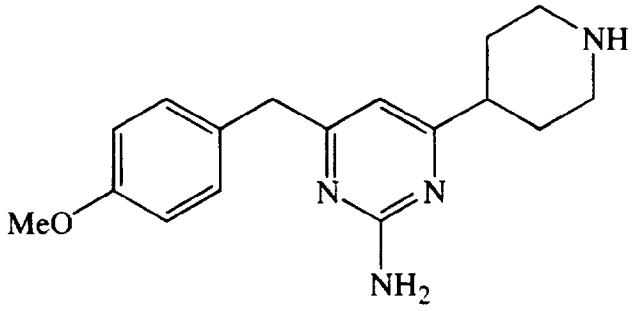
By a procedure similar to that described in Example 11(1) and crystallization from methanol, the

titled compound (4.8 g) was prepared from 2-amino-4-(1-benzyl-4-piperidinyl)-6-phenylpyrimidine (7 g, 20 mmol) obtained in Example 1 (2).

Melting point: 165-170°C

^{1}H-NMR ($CDCl_3$): δ 1.73 (3H, m), 1.92 (2H, m), 2.66 (1H, m), 2.75 (2H, dt, J=2.6, J=12.2), 3.12 (2H, m), 5.04 (2H, brs), 6.94 (1H, s), 7.46 (3H, m), 7.97 (2H, m)

(2) 2-Amino-4-(4-methoxyphenylmethyl)-6-(4-piperidinyl)pyrimidine

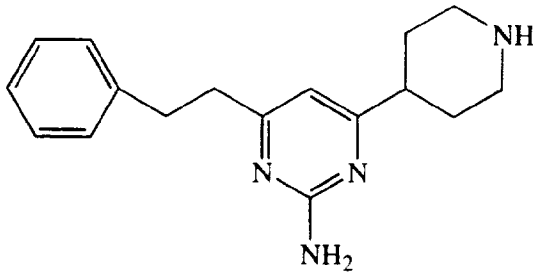


By a procedure similar to that described in Example 11(1) and crystallization from isopropyl alcohol-diethyl ether, the titled compound (8.81 g) was prepared from 2-amino-4-(1-benzoyl-4-piperidinyl)-6-(4-methoxyphenyl-methyl)pyrimidine (15 g, 37 mmol) obtained in Example 2 (3).

Melting point: 112-113°C

^{1}H-NMR ($CDCl_3$): δ 1.57 (3H, m), 1.79 (2H, m), 2.50 (1H, m), 2.67 (2H, dt, J=12.2, J=2.3), 3.14 (2H, m), 3.80 (3H, s), 3.83 (2H, s),4.96 (2H, brs), 6.28 (1H, s), 6.85 (2H, d,J=8.9), 7.16 (2H, d, J=8.9)

(3) 2-Amino-4-(2-phenylethyl)-6-(4-piperidinyl)-pyrimidine

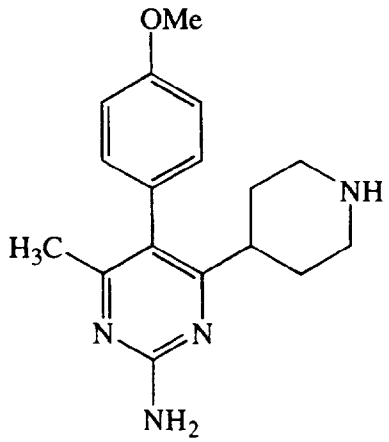


By a procedure similar to that described in Example 11(1) and crystallization from isopropyl alcohol-diethyl ether, the titled compound (10.8 g) was prepared from 2-amino-4-(1-benzyl-4-piperidinyl)-6-(2-phenylethyl)pyrimidine (22 g, 57 mmol) obtained in Example 4(2).

Melting point: 205°C (decomposed)

^{1}H-NMR (DMSO-d_6): δ 1.84 (4H, m), 2.73 (3H, m), 2.92 (4H, m), 3.28 (2H, d, J=12.5), 6.36 (1H, s), 6.50 (2H, s), 7.23 (5H, m), 8.99 (1H, brs)

(4) 2-Amino-4-methyl-5-(4-methoxyphenyl)-6-(4-piperidinyl)pyrimidine



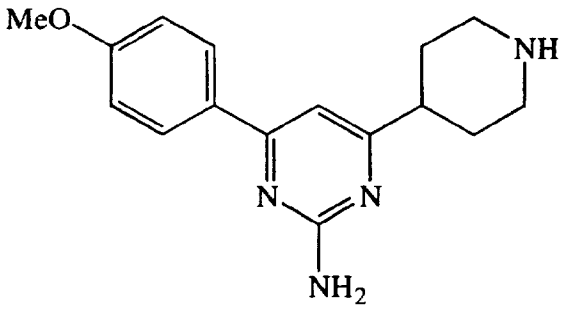
By a procedure similar to that described in Example 11(1) and crystallization from isopropanol-

diethyl ether, the titled compound (1.24 g) was prepared from 2-amino-4-(1-benzoyl-4-piperidinyl)-5-(4-methoxyphenyl)-6-methylpyrimidine (1.9 g, 4.7 mmol) obtained in Example 3.

Melting point: 191-192°C

^{1}H-NMR ($CDCl_3$): δ 1.71 (5H, m), 2.06 (3H, s), 2.45 (3H, m), 3.04 (2H, m), 3.87 (3H, s), 4.87 (2H, brs),6.99 (4H, m).

(5) 2-Amino-4-(4-methoxyphenyl)-6-(4-piperidinyl)-pyrimidine

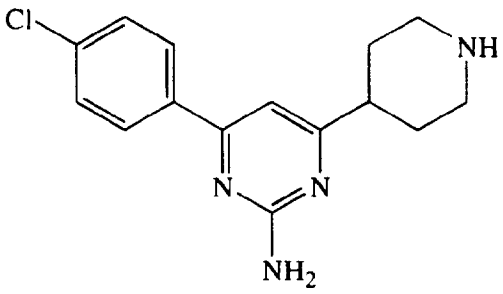


By a procedure similar to that described in Example 11(1) and crystallization from isopropanol, the title compound (3.73 g) was prepared from 2-amino-4-(1-benzoyl-4-piperidinyl)-6-(4-methoxyphenyl)pyrimidine(7.0 g, 0.018 mol) obtained in Example 5(2).

Melting point: 185-187°C

^{1}H-NMR ($CDCl_3$): δ 1.73 (3H, m), 1.92 (2H, m), 2.64 (1H, m), 2.74 (2H, m), 3.21 (2H, m), 3.87 (3H, s), 5.03 (2H, brs), 6.89 (1H, s), 6.98 (2H, d, J=8.6), 7.96 (2H, d, J=8.6).

(6) 2-Amino-4-(4-chlorophenyl)-6-(4-piperidinyl)-pyrimidine

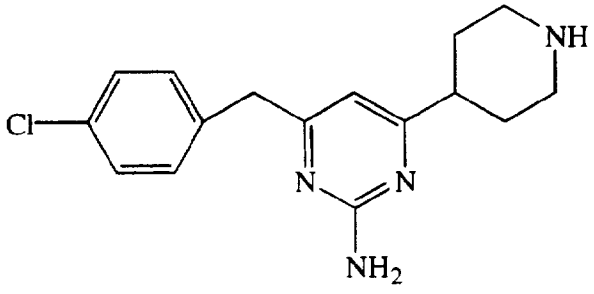


By a procedure similar to that described in Example 11(1) and crystallization from isopropanol, the titled compound (4.47 g) was prepared from 2-amino-4-(1-benzoyl-4-piperidinyl)-6-(4-chlorophenyl)pyrimidine (7.0 g, 0.018 mol) obtained in Example 6(2).

Melting point: 205-207°C

^{1}H-NMR ($CDCl_3$): δ 1.72 (3H, m), 1.91 (2H, m), 2.74 (3H, m), 3.21 (2H, m), 5.07(2H, brs), 6.90 (1H, s), 7.43 (2H, d, J=8.6), 7.93 (2H, d, J=8.6).

(7) 2-Amino-4-(4-chlorophenylmethyl)-6-(4-piperidinyl)-pyrimidine



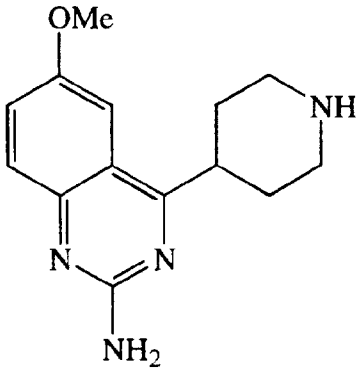
By a procedure similar to that described in Example 11(1) and crystallization from ethanol-diethyl ether, the title compound (3.01 g) was prepared from 2-

amino-4-(1-benzoyl-4-piperidinyl)-6-(4-chlorophenyl-methyl) pyrimidine (5.3 g, 0.013 mol) obtained in Example 7(2).

Melting point: 147-147.5°C

^{1}H-NMR ($CDCl_3$): δ 1.60 (3H, m), 1.80 (2H, m), 2.51 (1H, m), 2.68 (2H, dt, J=2.6, 12.2), 3.15 (2H, m), 3.84 (2H, s), 5.00 (2H, brs), 6.27 (1H, s), 7.17 (2H, d, J=8.6), 7.27 (2H, d, J=8.6).

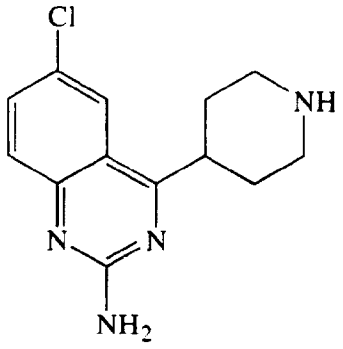
(8) 2-Amino-6-methoxy-4-(4-piperidinyl)quinazoline



By a procedure similar to that described in Example 11(1), the titled compound (2.60 g) was prepared from 2-amino-4-(1-benzoyl-4-piperidinyl)-6-methoxyquinazoline (4.15 g, 0.011 mol) obtained in Example 9(2).

Melting point: 213-216°C

(9) 2-Amino-6-chloro-4-(4-piperidinyl)-quinazoline



By a procedure similar to that described in Example 11(1), the title compound (440 mg) was prepared from 2-amino-4-(1-benzoyl-4-piperidinyl)-6-chloroquinazoline (477 mg, 1.2 mmol) obtained in Example 10(2).

^{1}H-NMR ($CDCl_3$): δ 1.85-2.00 (4H, m), 2.85 (2H, m), 3.25 (2H, m), 3.45 (1H, m), 5.10 (2H, brs), 7.58 (2H, s), 7.90 (1H, d, J=2.3).

(10) The compounds shown in Tables 3-5 were prepared by a procedure similar to that described in Example 12 and Example 13 treating the piperidinyl derivatives obtained hereinabove such as 2-amino-4-(4-piperidinyl)quinazoline, 2-amino-6-methoxy-4-(4-piperidinyl)-quinazoline, 2-amino-6-chloro-4-(4-piperidinyl)-quinazoline, 2-amino-4-phenyl-6-(4-piperidinyl)pyrimidine, 2-amino-4-(4-methoxyphenyl)-6-(4-piperidinyl)pyrimidine, 2-amino-4-(4-chlorophenyl)-6-(4-piperidinyl)-pyrimidine, 2-amino-4-methyl-5-(4-methoxyphenyl)-6-(4-piperidinyl)pyrimidine, 2-amino-4-(4-methoxyphenylmethyl)-6-(4-piperidinyl)pyrimidine, 2-amino-4-(4-chlorophenylmethyl)-6-(4-piperidinyl)-pyrimidine, 2-amino-4-(2-phenylethyl)-6-(4-piperidinyl)-

pyrimidine with various acid chlorides or carboxylic acids.

The acid chlorides may be prepared from the corresponding carboxylic acids in a conventional method well known to a skilled person in the art of organic chemistry, or some of them are commercially available.

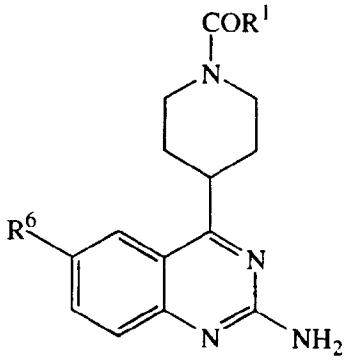


Table 3

Example No	R^5	R^6	Yield (%)	M.P. (°C)
14	cyclohexyl	H	65	203-204
15	cyclohexylmethyl		77	195-196
16	$-CH_2CH_3$		65	229-230
17	$-(CH_2)_2CH_3$		62	222-223
18	$-(CH_2)_3CH_3$		65	216-217
19	$-(CH_2)_4CH_3$		72	152-155
20	$-(CH_2)_5CH_3$		84	amorphous
21	$-(CH_2)_6CH_3$		77	amorphous
22	$-(CH_2)_7CH_3$		68	amorphous
23	$-(CH_2)_8CH_3$		84	87-90
24	$-(CH_2)_9CH_3$		90	91-92
25	i-Propyl		85	217-218
26	t-Butyl		98	249-253
27	$-(CH_2)_6NHBoc$		95	amorphous
28	$-(CH_2)_7NHBoc$		72	amorphous
29	$-(CH_2)_{10}NHBoc$		96	amorphous
30	$-(CH_2)_9OH$		80	117-118
31	$-CH_2OCH_3$		48	180-181
32	2-methoxyphenyl		84	254-256
33	3-methoxyphenyl		87	amorphous
34	4-methoxyphenyl		80	172-172.5
35	2-chlorophenyl		60	amorphous
36	3-chlorophenyl		86	amorphous
37	4-chlorophenyl		93	200.5-202
38	2-nitrophenyl		97	amorphous

(continued)

Example No	R^5	R^6	Yield (%)	M.P. (°C)
39	3-nitrophenyl	H	99	amorphous
40	4-nitrophenyl		87	203-204
41	2-fluorophenyl		96	193-195
42	3-fluorophenyl		99	amorphous
43	4-fluorophenyl		83	amorphous
44	2-methylphenyl		88	213-214
45	3-methylphenyl		86	178-179
46	4-methylphenyl		86	230-231
47	2-furyl		69	217-218
48	3-furyl		59	215-216
49	2-pyridyl		60	235-236
50	3-pyridyl		96	177-179
51	4-pyridyl		94	220-222
52	2,3-dimethoxyphenyl		85	205-207
53	2,4-dimethoxyphenyl		24	250-252
54	2,5-dimethoxyphenyl		69	201-203
55	2,6-dimethoxyphenyl		76	232-234
56	3,4-dimethoxyphenyl		71	173-175
57	3,5-dimethoxyphenyl		86	173-174
58	2,3-dichlorophenyl		79	256-258
59	2,4-dichlorophenyl		92	196-197
60	2,5-dichlorophenyl		97	125-128
61	2,6-dichlorophenyl		20	232-234
62	3,4-dichlorophenyl		100	192-193
63	3,5-dichlorophenyl		93	144-146

(continued)

Example No	R^5	R^6	Yield (%)	M.P. (°C)
64	2,4-dinitrophenyl	H	62	204-206
65	3,4-methylene-dioxyphenyl		45	197-198
66	1-naphthyl		84	214-215
67	2-naphthyl		81	230-231
68	2,3,4-trimethoxy-phenyl		57	amorphous
69	2,3,6-trimethoxy-phenyl		57	230-231.5
70	2,4,5-trimethoxy-phenyl		31	105-108
71	2,4,6-trimethoxy-phenyl		29	125-127
72	3,4,5-trimethoxy-phenyl		88	199-202
73	2,3,5-trichloro-phenyl		87	241-242
74	2,3,6-trichloro-phenyl		33	225-227
75	2,4,6-trichloro-phenyl		40	213-214
76	benzyl		53	225-226
77	2-methoxybenzyl		97	amorphous
78	3-methoxybenzyl		100	amorphous
79	4-methoxybenzyl		90	220-221
80	2-chlorobenzyl		99	187-188
81	3-chlorobenzyl		92	190-191
82	4-chlorobenzyl		89	206-207
83	2-fluorobenzyl		98	204-205
84	3-fluorobenzyl		89	207.5-209
85	4-fluorobenzyl		96	196-198
86	2-nitrobenzyl		79	202-203
87	3-nitrobenzyl		99	amorphous

(continued)

Example No	R^5	R^6	Yield (%)	M.P. (°C)
88	4-nitrobenzyl	H	94	205-206
89	2-pyridylmethyl		77	168-170
90	3-pyridylmethyl		99	232-235
91	2,5-dimethoxy-benzyl		94	147-148
92	3,4-dimethoxy-benzyl		98	158-159
93	3,5-dimethoxy-benzyl		95	108-110
94	2,4-dichlorobenzyl		84	224-225
95	2,6-dichlorobenzyl		80	202-203
96	3,4-dichlorobenzyl		98	149-150
97	2,4-dinitrobenzyl		69	229-231
98	2,3,6-trichloro-benzyl		80	208-209
99	3,4,5-trimethoxy-benzyl		49	188-189
100	2-phenylethyl		69	amorphous
101	2-(3,4-methylene-dioxyphenyl)ethyl		71	160-163
102	3-phenylpropyl		58	amorphous
103	$-(CH_2)_5CH_3$	OCH_3	82	124-125
104	$-(CH_2)_6CH_3$		90	138-139
105	$-(CH_2)_7CH_3$		82	104-106
106	$-(CH_2)_8CH_3$		74	84-86
107	$-(CH_2)_9CH_3$		81	94-96
108	2-methoxyphenyl		100	196-197
109	3-methoxyphenyl		98	amorphous
110	4-methoxyphenyl		100	201-202
111	2-chlorophenyl		100	201-202

(continued)

Example No	R^1	R^6	Yield (%)	M.P. (°C)
112	3-chlorophenyl	OCH_3	100	186-187
113	4-chlorophenyl		88	218-221
114	2-nitrophenyl		100	218-220
115	3-nitrophenyl		95	240-242
116	4-nitrophenyl		60	210-212
117	3,4-methylenedioxy-phenyl		71	260 dec. (hydro-chloride)
118	2-methoxybenzyl		97	amorphous
119	3-methoxybenzyl		64	150-152
120	4-methoxybenzyl		67	165-167
121	2-chlorobenzyl		100	173-174
122	3-chlorobenzyl		80	172-173
123	4-chlorobenzyl		100	179-180
124	2-nitrobenzyl		93	215-218
125	3-nitrobenzyl		89	195-196.5
126	4-nitrobenzyl		100	198-199
127	$-(CH_2)_6CH_3$	Cl	62	135-136
128	$-(CH_2)_7CH_3$		52	225-228
129	$-(CH_2)_8CH_3$		56	230-233
130	3,4-methylene-dioxyphenyl		41	250 dec. (hydrochloride)
131	4-methoxybenzyl		60	193-195
132	4-chlorobenzyl		60	188-192
133	4-nitrobenzyl		26	233 dec.

(continued)

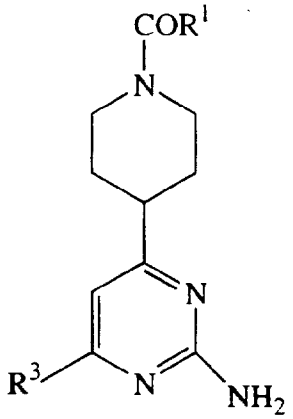


Table 4

Example No	R^1	R^3	Yield (%)	M.P. (°C)
134	cyclohexyl	Ph	88	amorphous
135	cyclohexylmethyl		76	amorphous
136	$-(CH_2)_6CH_3$		89	112-113
137	$-(CH_2)_7CH_3$		100	140-141 (hydrochloride)
138	$-(CH_2)_8CH_3$		100	amorphous
139	2-furyl		77	122-123
140	3,4-methylene-dioxyphenyl		77	201-202
141	benzyl		74	141-142
142	4-methoxybenzyl		100	amorphous
143	4-chlorobenzyl		100	157-158
144	4-nitrobenzyl		100	amorphous
145	3,4-methylene-dioxybenzyl		68	amorphous
146	3,4,5-trimethoxybenzyl		48	98-100
147	$-(CH_2)_6CH_3$	4-chloro-phenyl	93	118-120
148	$-(CH_2)_7CH_3$		92	97-98
149	$-(CH_2)_8CH_3$		94	108-109
150	3,4-methylene-dioxyphenyl		84	103-106

(continued)

Example No	R^2	R^3	Yield (%)	M.P. (°C)
151	4-methoxybenzyl	4-chloro-phenyl	99	178.5-180
152	4-chlorobenzyl		89	183-184
153	4-nitrobenzyl		94	200-202
154	$-(CH_2)_6CH_3$	4-meth-oxy-phenyl	93	118-120
155	$-(CH_2)_7CH_3$		92	97-98
156	$-(CH_2)_8CH_3$		94	108-109
157	3,4-methylene-dioxyphenyl		84	103-106
158	4-methoxybenzyl		99	178.5-180
159	4-chlorobenzyl		89	183-184
160	4-nitrobenzyl		94	200-202
161	cyclohexyl	4-meth-oxy-benzyl	76	159-160
162	$-CH_3$		89	203-205
163	$-CH_2CH_3$		93	133-135
164	$-(CH_2)_2CH_3$		98	140-141
165	$-(CH_2)_3CH_3$		94	100-103
166	$-(CH_2)_4CH_3$		100	120-121
167	$-(CH_2)_5CH_3$		100	108-109
168	$-(CH_2)_6CH_3$		98	101-103
169	$-(CH_2)_7CH_3$		100	114-116
170	$-(CH_2)_8CH_3$		100	102-104
171	$-(CH_2)_9CH_3$		100	88-90
172	i-Propyl		100	163-163.5
173	t-Butyl		96	151-152
174	$-(CH_2)_2Cl$		91	131-134
175	$-(CH_2)_2Br$		96	90-91

(continued)

Example No	R^1	R^3	Yield (%)	M.P. (°C)
176	$-(CH_2)_2NHBoc$	4-methoxybenzyl	100	amorphous
177	$-(CH_2)_2OH$		59	amorphous
178	2-methoxyphenyl		100	161-162
179	3-methoxyphenyl		100	149-151
180	4-methoxyphenyl		100	169-170.5
181	2-chlorophenyl		100	170-171.5
182	3-chlorophenyl		100	141-142
183	4-chlorophenyl		100	188-189
184	2-nitrophenyl		100	161-162
185	3-nitrophenyl		100	153-155 (hydrochloride)
186	4-nitrophenyl		100	amorphous (hydrochloride)
187	2-fluorophenyl		100	181-183
188	3-fluorophenyl		100	168-170.5
189	4-fluorophenyl		94	176-177
190	2-methylphenyl		99	147-148.5
191	3-methylphenyl		93	175-176
192	4-methylphenyl		99	183-184
193	2-furyl		83	124-125
194	2-pyridyl		81	157-158
195	3-pyridyl		45	153.5-154.5
196	4-pyridyl		100	148-150
197	2,3-dimethoxyphenyl		86	147-148
198	2,4-dimethoxyphenyl		39	194-196
199	2,5-dimethoxyphenyl		59	135-136
200	2,6-dimethoxyphenyl		100	144-145

(continued)

Example No	R^1	R^3	Yield (%)	M.P. (°C)
201	3,4-dimethoxyphenyl	4-methoxybenzyl	99	159-160
202	3,5-dimethoxyphenyl		100	198-200
203	2,3-dichlorophenyl		100	157-158
204	2,4-dichlorophenyl		100	147-148
205	2,5-dichlorophenyl		100	155-156
206	2,6-dichlorophenyl		85	178-179
207	3,4-dichlorophenyl		98	195-196
208	3,5-dichlorophenyl		100	154-155
209	2,4-dinitrophenyl		89	116-119
210	3,4-methylenedioxyphenyl		96	170-171
211	1-naphtyl		78	161-162
212	2-naphtyl		79	220-221.5
213	2,3,4-trimethoxyphenyl		50	123-125
214	2,3,6-trimethoxyphenyl		90	amorphous
215	2,4,5-trimethoxyphenyl		35	189-190
216	2,4,6-trimethoxyphenyl		73	amorphous
217	3,4,5-trimethoxyphenyl		94	amorphous
218	2,3,5-trichlorophenyl		100	189-190
219	2,3,6-trichlorophenyl		89	amorphous
220	2,4,6-trichlorophenyl		100	159-160
221	benzyl		68	140-140.5
222	2-methoxybenzyl		96	134-136
223	3-methoxybenzyl		57	179-180
224	4-methoxybenzyl		100	129-130
225	2-chlorobenzyl		100	190-193

(continued)

Example No	R^1	R^3	Yield (%)	M.P. (°C)
226	3-chlorobenzyl	4-methoxybenzyl	97	178-181
227	4-chlorobenzyl		92	158-159.5
228	2-flurobenzyl		100	170-171
229	3-fluorobenzyl		100	156-158.5
230	4-fluorobenzyl		99	159-160
231	2-nitrobenzyl		100	198-200
232	3-nitrobenzyl		100	162-164
233	4-nitrobenzyl		94	149-150
234	2-pyridylmethyl		74	131-132
235	3-pyridylmethyl		48	109-112
236	2,5-dimethoxybenzyl		97	130-132
237	3,4-dimethoxybenzyl		100	amorphous
238	3,5-dimethoxybenzyl		91	amorphous
239	2,4-dichlorobenzyl		100	182-184
240	2,6-dichlorobenzyl		99	amorphous
241	3,4-dichlorobenzyl		93	150-151
242	2,4-dinitrobenzyl		96	131-132
243	3,4-methylenedioxybenzyl		86	155-156
244	2,3,6-trichlorobenzyl		100	amorphous
245	3,4,5-trimethoxybenzyl		96	amorphous
246	2-(3,4-methylenedioxyphenyl)ethyl		71	123-125
288	1,3-benzo-dioxol-4-yl		82	167-167.5
289	5-benzimidazolyl		81	amorphous
290	5-indolyl		93	amorphous
291	1,4-benzo-dioxan-6-yl		92	187-188
292	3,4-difluorophenyl		69	159-160
293	5-benzo[b]furanyl		77	188-188.5
294	6-benzo[b]furanyl		88	186-187
295	4-benzo[b]furanyl		90	173-174
296	2,3-dihydrobenzo-[b]furan-5-yl		98	162-164
297	5-benzoxazolyl		88	178-179
298	6-benzoxazolyl		83	185-186
299	6-benzothiazolyl		75	153-154
300	4-hydroxy-3-methoxyphenyl		88	131-135 (hydrochloride)
301	3-hydroxy-4-methoxyphenyl		96	amorphous (hydrochloride)

(continued)

Example No	R^1	R^6	Yield (%)	M.P. (°C)
247	$-(CH_2)_6CH_3$	4-chloro-benzyl	70	142-143
248	$-(CH_2)_7CH_3$		79	137.5-138.5
249	$-(CH_2)_8CH_3$		70	136-137
250	3,4-methylene-dioxyphenyl		85	162-163
251	4-methoxybenzyl		82	132-133
252	4-chlorobenzyl		77	163-164
253	3,4-methylene-dioxybenzyl		89	203-204
254	cyclohexyl	2-phenyl-ethyl	78	120-121
255	$-(CH_2)_6CH_3$		99	83-84
256	$-(CH_2)_7CH_3$		94	72-73
257	$-(CH_2)_8CH_3$		92	77-78
258	2-furyl		84	109-110
259	3,4-methylene-dioxyphenyl		85	158-158.5
260	benzyl		47	amorphous
261	4-methoxybenzyl		81	135-136
262	4-chlorobenzyl		80	144-145.5
263	4-nitrobenzyl		91	169-170

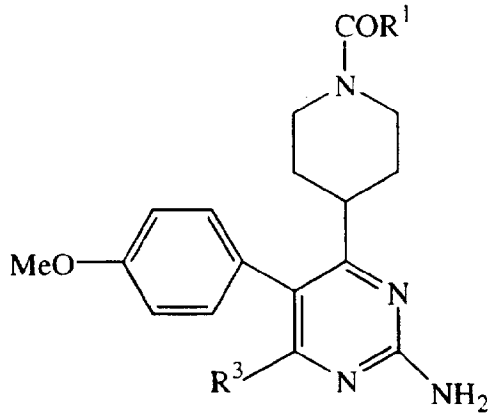
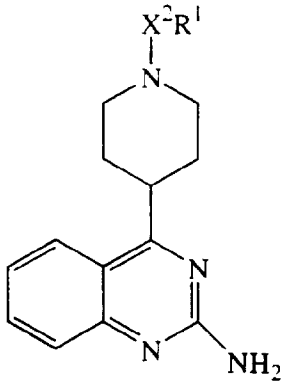


Table 5

Example No.	R^1	Yield (%)	M.P. (°C)
264	cyclohexyl	74	225-226
265	2-furyl	82	236-237
266	3,4-methylene-dioxyphenyl	97	220-222
267	benzyl	61	196-197

Example 268-277

The urethane and sulfonamide derivatives in Tables 6 and 7 were prepared by a procedure similar to that described in Example 12, treating various chloroformates or sulfonyl chlorides instead of acid chlorides with piperidinyl derivatives, i.e., 2-amino-4-(4-piperidinyl)quinazoline and 2-amino-4-(4-methoxyphenylmethyl)-6-(4-piperidinyl)pyrimidine.



Example 268-277

Table 6

Example No.	X^2	R^1	Yield (%)	M.P. (°C)
268	-(CO)O-	-Ph	93	amorphous
269		$-CH_2Ph$	90	148-150
270	$-SO_2-$	$-(CH_2)_7CH_3$	57	144-145
271		-Ph	89	212-214
272		$-CH_2Ph$	48	234-235

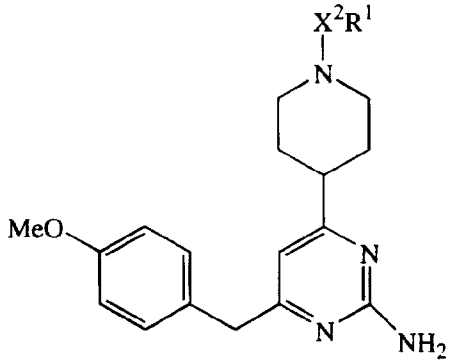
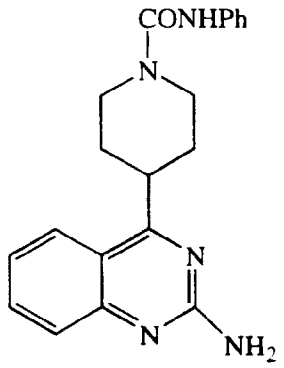


Table 7

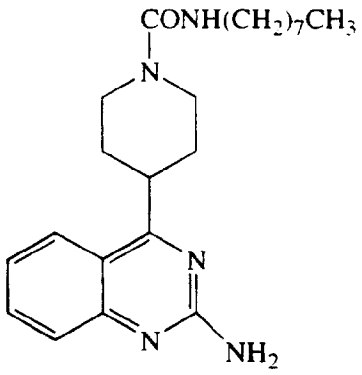
Example No.	X^2	R^1	Yield (%)	M.P. (°C)
273	-(CO)O-	-Ph	72	164-166
274		$-CH_2Ph$	61	160-161
275	$-SO_2-$	$-(CH_2)_7CH_3$	55	135-136
276		-Ph	84	156-157.5
277		$-CH_2Ph$	60	177-178

Example 278 Synthesis of 2-amino-4-(1-phenylcarbamoyl-4-piperidinyl)quinazoline



To a solution of 2-amino-4-(4-piperidinyl)-quinazoline (100 mg, 0.44 mmol) obtained in Example 11(1) and triethylamine (133 mg, 1.3 mmol) in dichloromethane (50 ml) was added phenyl isocyanate (50 mg, 0.42 mmol) under a nitrogen atmosphere. The mixture was stirred for about 3 hours at room temperature. The reaction mixture was washed with saturated sodium hydrogencarbonate aqueous solution. The organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was purified by silicagel column chromatography (chloroform: methanol = 99:1) to give the titled compound (127 mg). Melting point: 178-180°C

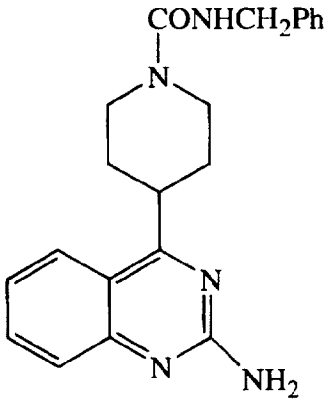
Example 279 Synthesis of 2-amino-4-(1-octylcarbamoyl-4-piperidinyl)quinazoline



By a procedure similar to that described in Example 278, the titled compound (122 mg) was prepared from 2-amino-4-(4-piperidinyl)quinazoline (100 mg, 0.44 mmol) obtained in Example 11(1).

Melting point: 85-87°C

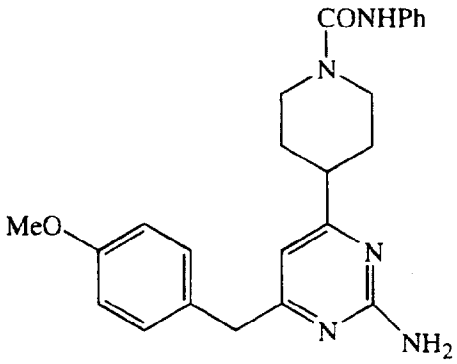
Example 280 Synthesis of 2-amino-4-(1-benzyl-carbamoyl-4-piperidinyl)quinazoline



By a procedure similar to that described in Example 278, the titled compound (132 mg) was prepared from of 2-amino-4-(4-piperidinyl)quinazoline (100 mg, 0.44 mmol) obtained in Example 11(1).

Melting point: 217-218°C

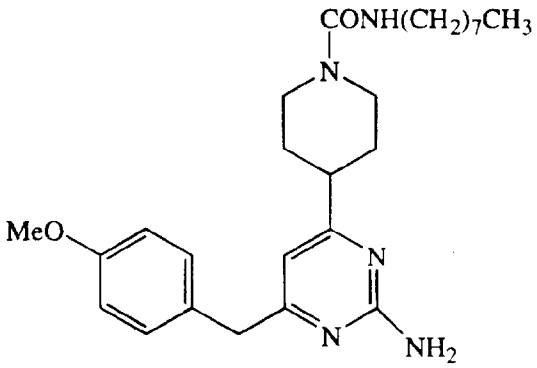
Example 281 Synthesis of 2-amino-4-(4-methoxyphenylmethyl)-6-(1-phenylcarbamoyl-4-piperidinyl)-pyrimidine



By a procedure similar to that described in Example 278, the titled compound (108 mg) was prepared from 2-amino-4-(4-methoxyphenylmethyl)-6-(4-piperidinyl)-pyrimidine (100 mg, 0.34 mmol).

Melting point: 178-180°C

Example 282 Synthesis of 2-amino-4-(4-methoxyphenylmethyl)-6-(1-octylcarbamoyl-4-piperidinyl)pyrimidine

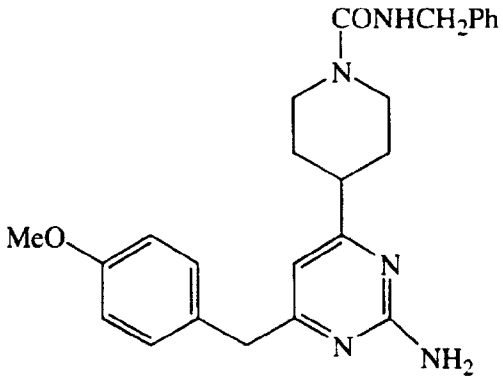


By a procedure similar to that described in Example 278, the titled compound (120 mg) was prepared from of 2-amino-4-(4-methoxyphenylmethyl)-6-(4-

piperidinyl)pyrimidine(100 mg, 0.34 mmol).

Melting point: 104-106°C

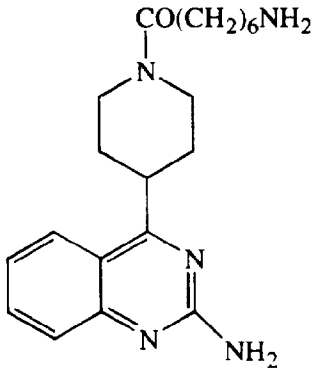
Example 283 Synthesis of 2-amino-4-(1-benzylcarbamoyl-4-piperidinyl)-6-(4-methoxyphenylmethyl)pyrimidine



By a procedure similar to that described in Example 278, the titled compound (119 mg) was prepared from of 2-amino-4-(4-methoxyphenylmethyl)-6-(4-piperidinyl)pyrimidine (100 mg, 0.34 mmol).

Melting point: 128-131°C

Example 284 Synthesis of 2-amino-4-[1-(7-aminoheptanoyl)-4-piperidinyl]quinazoline

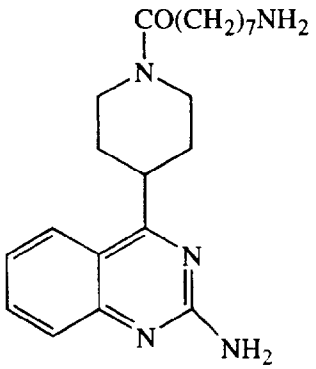


To a solution of 2-amino-4-[1-(7-t-butoxy-

carbonylaminoheptanoyl)-4-piperidinyl]quinazoline (160 mg) obtained in Example 27 in tetrahydrofuran (1 ml) was added 4 N hydrogen chloride-dioxane solution (1 ml). The reaction mixture was stirred for about 1 hour at room temperature and was evaporated. The residue was triturated with diethyl ether to give the title compound (131 mg) as hydrochloride.

Melting point: 230-233°C

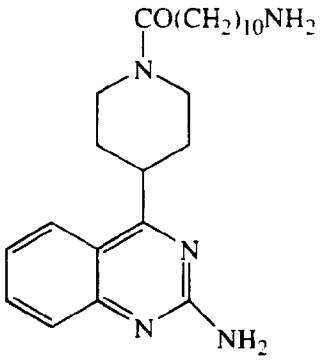
Example 285 Synthesis of 2-amino-4-[1-(8-amino-octanoyl)-4-piperidinyl]quinazoline



By a procedure similar to that described in Example 284, the titled compound (91 mg) as hydrochloride was prepared from 2-amino-4-[1-(8-t-butoxycarbonylamino-octanoyl)-4-piperidinyl]quinazoline (100 mg) obtained in Example 28.

Melting point: 222-224°C

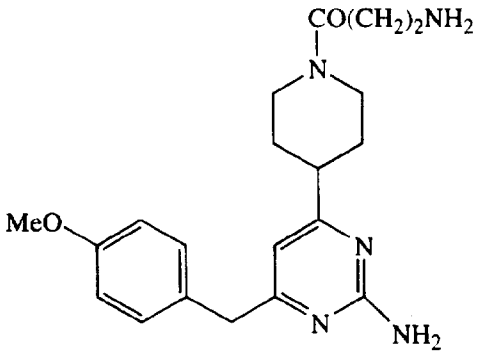
Example 286 Synthesis of 2-amino-4-[1-(11-aminoundecanoyl)-4-piperidinyl]quinazoline



By a procedure similar to that described in Example 284, the titled compound (130 mg) as hydrochloride was prepared from 2-amino-4-[1-(11-t-butoxycarbonylaminoundecanoyl)-4-piperidinyl]quinazoline (170 mg) obtained in Example 29.

Melting point: 163-165°C

Example 287 Synthesis of 2-amino-4-[1-(3-amino-propanoyl)-4-piperidinyl]-6-(4-methoxyphenyl-methyl)pyrimidine



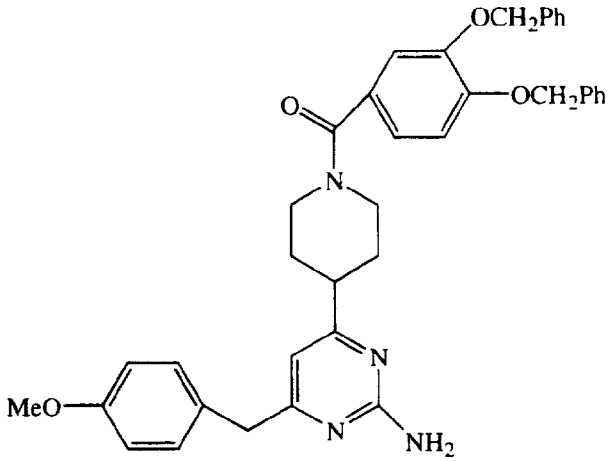
By a procedure similar to that described in Example 284, the titled compound (127 mg) as hydrochloride was prepared from 2-amino-4-[1-(3-t-butoxycarbonylaminopropanoyl)-4-piperidinyl]-6-(4-methoxyphenylmethyl)pyrimidine (170 mg) obtained in

Example 176.

Melting point: amorphous

Example 302 Synthesis of 2-amino-4-[1-(3,4-dihydroxybenzoyl)-4-piperidinyl]-6-(4-methoxyphenylmethyl)-pyrimidine

(1) 2-Amino-4-[1-(3,4-dibenzyloxybenzoyl)-4-piperidinyl]-6-(4-methoxyphenylmethyl) pyrimidine

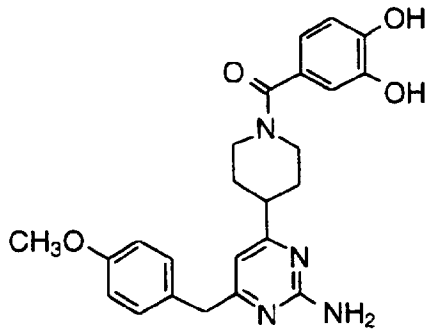


To a solution of 2-amino-4-(4-methoxyphenylmethyl)-6-(4-piperidinyl)pyrimidine (160 mg, 0.54 mmol), 3,4-dibenzyloxybenzoic acid (179 mg, 0.54 mmol) and 1-hydroxybenzotriazole (72 mg, 0.54 mmol) in dichloromethane (150 ml) were added 1-ethyl-3-(N, N'-dimethylaminopropyl)carbodiimide hydrochloride (103 mg, 0.54 mmol) at room temperature under nitrogen atmosphere. After stirring for about 30 minutes, the mixture was washed successively with saturated sodium hydrogen carbonate solution and brine. The organic layer was dried over anhydrous sodium sulfate and then evaporated. The residue was purified by column chromatography (chloroform : methanol = 99 : 1) to give the titled

compound (477 mg).

^{1}H-NMR ($CDCl_3$): δ 1.77 (4H, m), 2.59 (1H, m), 2.84 (2H, m), 3.78 (3H, s), 3.82 (2H, s), 3.90 (1H, m), 4.70 (1H, m), 5.11 (2H, s), 5.17 (2H, s), 5.18 (2H,s), 6.24 (1H, s), 6.84-7.00 (5H, m), 7.14-7.44 (12H, m).

(2) 2-Amino-4-[1-(3,4-dihydroxybenzoyl)-4-piperidinyl]-6-(4-methoxyphenylmethyl) pyrimidine

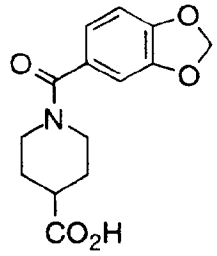


2-Amino-4-[1-(3,4-dibenzyloxybenzoyl)-4-piperidinyl]-6-(4-methoxyphenylmethyl)pyrimidine (293 mg, 0.48 mmol) was dissolved in a mixture of methanol (3 ml) and ethyl acetate (3 ml), and hydrogenated under 1 atm in the presence of 10% palladium on carbon (80 mg) for about 3 hours. The catalyst was filtered off and washed with methanol. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (chloroform : methanol = 97 : 3) to give the titled compound (155 mg).

^{1}H-NMR ($CDCl_3$): δ 1.74 (4H, m), 2.62 (1H, m), 2.87 (2H, m), 3.77 (3H, s), 3.82 (2H, s), 3.87 (1H, m), 4.65 (1H, m), 5.35 (2H, s), 6.25 (1H, s), 6.79 (5H, m), 7.14 (2H, d, J=8.6), 7.26 (2H, s).

Example 303 Synthesis of 2-amino-4-(4-bromophenylmethyl)-6-[1-(3,4-methylenedioxybenzoyl)-4-piperidinyl] pyrimidine

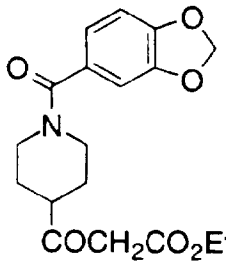
(1) 1-(3,4-Methylenedioxybenzoyl)isonipecotic acid



To an ice cold solution of isonipecotic acid (119.77 g, 0.927mol) and potassium carbonate (256.32 g, 1.855mol) in water (900 ml) was added dropwise piperonyloyl chloride (155.6 g, 0.843mol) in tetrahydrofuran (900ml) with vigorous stirring over about 2 hours. The reaction temperature was kept below about 10°C during the addition and the mixture was then stirred for about 30 minutes. The reaction mixture was acidified with conc. hydrochloric acid and extracted with chloroform. The organic layer was washed with water and dried over anhydrous magnesium sulfate, then evaporated. The residue was crystallized from methanol to give the titled compound (210.81 g)

^{1}H-NMR ($CDCl_3$): δ 1.49(2H, m), 1.81(2H, m), 2.51(1H, m), 2.99(2H, m), 3.98(2H, m), 6.07(2H, s), 6.88(1H, dd, J=1.3, J=7.9), 6.95(2H, m), 12.29(1H, s).

(2) Ethyl 3-[1-(3,4-methylenedioxybenzoyl)-4-piperidinyl)]-3-oxopropionate

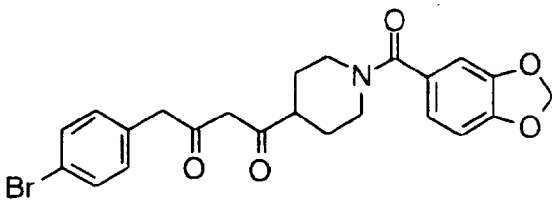


To a THF solution(2 L) of 1-(3,4-methylene-dioxybenzoyl)isonipecotic acid (110 g, 0.397 mol) was added carbonyldiimidazole (70.8 g, 0.437 mol) in several portions at room temperature under nitrogen atmosphere. After stirring for about 3.5 hours, magnesium ethyl malonate (125.12 g, 0.437 mol) was added and refluxed for about 3 hours. The solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (3 L) and saturated sodium hydrogen carbonate (1.5 L). The organic layer was washed with brine twice and dried over anhydrous magnesium sulfate, then evaporated. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 1) to give the titled compound as colorless oil (132.40 g).

Magnesium ethyl malonate was prepared as follows: To a stirred THF solution (1 L) of monoethyl malonate (183.18 g, 1.39 mol) was added magnesium ethoxide (79.54 g, 0.70 mol) in several portions. After about 4 hours, the solvent was removed under reduced pressure and the residue was reevaporated with toluene to give magnesium ethyl malonate (190.82 g).

(3) 4-{1-[4-(4-Bromophenyl)-1,3-dioxobutyl]}-1-(3,4-

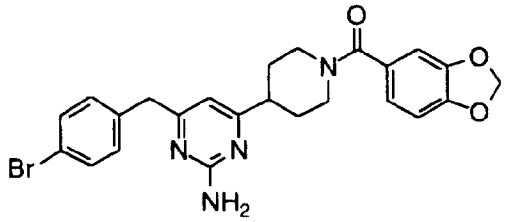
methylenedioxybenzoyl) piperidine



To an ice cooled solution of ethyl 3-[1-(3,4-methylenedioxybenzoyl)-4-piperidinyl]-3-oxo-propionate (7 g, 20 mmol) in tetrahydrofuran (35 ml) was added sodium hydride (60% oil dispersion, 1.68 g, 42 mmol) in several portions under nitrogen atmosphere. The reaction temperature was kept below about 5°C during addition and the mixture was stirred for about a further 30 minutes. To the mixture 4-bromophenylacetyl chloride (5.18 g, 0.22 mmol) in tetrahydrofuran (15 ml) was added dropwise over about one hour at about 5°C. After stirring about further 30 minutes, the mixture was acidified by 4 N-hydrochloric acid and was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate, then evaporated to give a diketoester as a crude oil. The diketoester was used following reaction without further purification. The mixture of diketoester, water (1.6 ml) and dimethylsufoxide (18 ml) was heated at about 110°C for about 7.5 hours. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate, then evaporated. The residue was purified by flash column chromatography (hexane : ethyl acetate = 1 : 1) to give the titled compound (5.54 g) as an oil.

^{1}H-NMR ($CDCl_3$) : δ 1.63(2H, m), 1.81(2H, m), 2.42(1H, m), 2.91(2H, m,), 3.57(2H, s), 3.9-4.9(2H,m), 5.43(1H, s), 6.00(2H, s), 6.86(3H, m), 7.10(2H, d, J=8.6), 7.47(2H, d, J=8.6), 15.37(1H, s).

(4) 2-Amino-4-(4-bromophenylmethyl)-6-[1-(3,4-methylenedioxybenzoyl)-4-piperidinyl]pyrimidine



A mixture of 4-{1-[4-(4-bromophenyl)-1,3-dioxobutyl]}-1-(3,4-methylenedioxybenzoyl) piperidine (5.3 g, 11.2 mmol), guanidine carbonate (2.02 g, 11.2 mmol) and pyridine (25 ml) was heated at about 110°C for about 8 hours. The mixture was evaporated in vacuo and the residue was partitioned between chloroform and saturated sodium hydrogen carbonate aqueous solution. The organic layer was washed with brine and dried over anhydrous sodium sulfate, then evaporated. Crystallization from ethanol gave the titled compound (3.88 g).

Melting point: 162-162.5°C

^{1}H-NMR ($CDCl_3$) : δ 1.65-1.84(4H, m), 2.66(1H, m), 2.92(2H, m), 3.83(2H, s), 4-4.8(2H,m), 4.96(2H, s), 6.00(2H, s), 6.26(1H, s), 6.82(1H, d, J=8.3), 6.93(2H, m), 7.12(2H, d, J=8.6), 7.44(2H, d, J=8.25).

The free amine (300 mg) was dissolved in chloroform and treated with 1 N hydrogen chloride-diethyl

ether solution (1 ml). The solvent was removed in vacuo. The residue was dissolved in small amount of isopropanol and triturated with ether to give the hydrochloride (300 mg) of the titled compound.

Example 304-314

The amide compounds shown in Table 8 were prepared by a similar method described in Example 303 using a reaction of ethyl 3-[1-(3,4-methylenedioxy-benzoyl)-4-piperidinyl)]-3-oxo-propionate with various carboxylic acids.

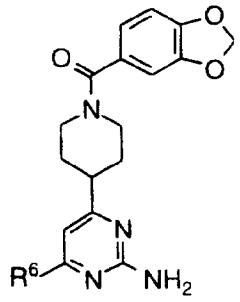
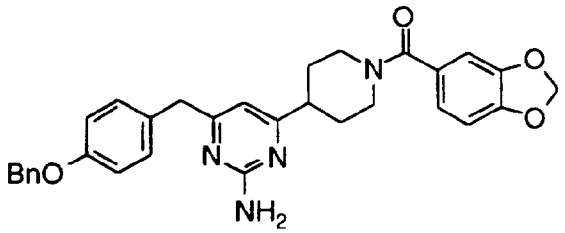


Table 8

Example No.	R^6	Yield (%)	M.P. (°C)
304	benzyl	39	115-118 (hydrochloride)
305	3-methoxybenzyl	68	amorphous (hydrochloride)
306	3,4-dimethoxybenzyl	55	150-151
307	2,5- dimethoxybenzyl	60	150-152
308	3,5- dimethoxybenzyl	52	146-149 (hydrochloride)
309	3,4,5- trimethoxybenzyl	26	154-155
310	2-chlorobenzyl	21	amorphous (hydrochloride)
311	3,4-dichlorobenzyl	31	169-170
312	2,4- dichlorobenzyl	32	205-206
313	2,6- dichlorobenzyl	35	213-214
314	3,4-methylenedioxybenzyl	58	amorphous (hydrochloride)

Example 315 Synthesis of 2-amino-4-(4-hydroxyphenyl-methyl)-6-[1-(3,4-methylenedioxybenzoyl)-4-piperidinyl] pyrimidine

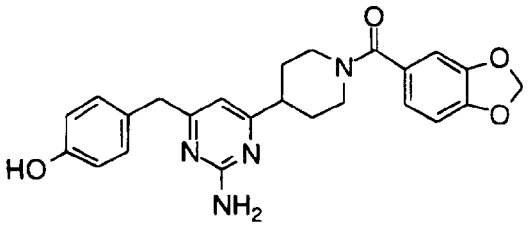
(1) 2-Amino-4-(4-benzyloxyphenylmethyl)-6-[1-(3,4-methylenedioxybenzoyl)-4-piperidinyl] pyrimidine



According to similar procedures described in Example 303 (3) and (4), the titled compound (570 mg) was prepared by treating ethyl 3-[1-(3,4-methylenedioxy-benzoyl)-4-piperidinyl)]-3-oxo-propionate(2.0 g) with 4-benzyloxyphenylacetyl chloride (1.66 g).

^{1}H-NMR ($CDCl_3$): δ 1.77 (4H, m), 2.65 (1H, m), 2.91 (2H, m), 3.83 (2H, s), 4-4.8 (2H, m), 4.93 (2H, s), 5.05 (2H, s), 5.99 (2H, s), 6.27 (1H, s), 6.81 (2H, d, J=8.1), 6.92 (3H, m), 7.15 (2H, d, J=8.6), 7.38 (5H, m).

(2) 2-Amino-4-(4-hydroxyphenylmethyl)-6-[1-(3,4-methylenedioxybenzoyl)-4-piperidinyl] pyrimidine



2-Amino-4-(4-benzyloxyphenylmethyl)-6-[1-(3,4-methylenedioxybenzoyl)-4-piperidinyl) pyrimidine (570 mg,

1.09 mmol) was dissolved in acetic acid (5 ml) and hydrogenated under 1 atm in the presence of 10% palladium on carbon (360 mg) for about 3.5 hours. The catalyst was filtered off. The filtrate was poured into aqueous sodium hydrogen carbonate and extracted with chloroform. The organic layer was concentrated in vacuo and the residue was purified by column chromatography (chloroform : methanol = 97 : 3) to give the titled compound (256 mg) as a foam.

^{1}H-NMR ($CDCl_3$): δ 1.85 (4H, m), 2.67 (1H m), 2.90 (2H, m), 3.80 (2H, s), 4.0-4.8 (2H, m), 5.10 (2H, s), 5.99 (2H, s), 6.30 (1H, s), 6.72 (2H, d, J=8.6), 6.81 (1H, d, J=8.3), 6.93 (2H, m), 7.02 (2H, d, J=8.6), 7.26 (1H, s).

The free amine (256 mg) was dissolved in chloroform and treated with 1N hydrogen chloride-diethyl ether solution (0.6 ml). The solvent was removed in vacuo. The residue was dissolved in small amount of isopropanol and triturated with ether to give the hydrochloride (240 mg) of the titled compound.
Melting point: 176-179 °C

Example 316 Inhibitory activity of TNFα Production

BALB/c mice (female, 5-7 weeks old, Charles River Japan, Tokyo, Japan) were injected i.p. with 1 ml of 2.4% thioglycollate broth. After 4 days, the mice were sacrificed. Peritoneal exudated cells (PEC's) were collected from the peritoneal cavity by washing with minimum essential medium (MEM, Handai biseibutubyou

kenkyukai, Osaka, Japan) containing 5 U/ml heparin, 1% fetal bovine serum (FBS, Filtron, Victoria, Australia) and antibiotics. The cells were washed two times with MEM, suspended with MEM containing 10% FBS (complete MEM, cMEM) and seeded into 96-well culture plates (Costar, Cambridge, MA, USA) at 2 x 10^5 cells/well. The cells were incubated for 1 hour at 37°C in a humidified 5% CO_2 incubator and washed two times to remove non-adherent cells.

TNFα was induced by 10 μg/ml of LPS (E. coli O111B4, DIFCO, Detroit, MI, USA) the cells were cultured for 18 hours at 37°C. A compound of the present invention was dissolved in DMSO and added to the culture simultaneously with LPS. The final DMSO concentration was below 0.1%. The TNFα concentration in supernatant and recombinant mouse TNFa standard (rm-TNFα, Genzyme, MA, USA) were incubated overnight at 4°C in a 96-well plate coated with anti-mouse TNFα monoclonal antibody (PharMingen, San Diego, CA, USA) that previously had been blocked with 10% FBS. Each well of the plate first was incubated at room temperature with biotinylated anti-mouse TNFα polyclonal antibodies (PharMingen) for 45 minutes, then with peroxidase-conjugated streptavidin (Kirkegaard & Perry Laboratories Inc., Gaitherburg, MD, USA) for 30 minutes. After each incubation, the plate was washed 4 to 8 times with PBS containing 0.2% Tween 20. TMB (Kirkegaard & Perry Laboratories Inc.) was the peroxidase substrate used, the absorbance of each well

was quantified at 450 nm by a microplatereader (Molecular Devices Corp., CA, USA). TNFα levels in the supernatant were quantified with rm-TNFα as the standard.

Inhibitory activity of TNFα production was also quantified using human peripheral blood mononuclear cells(PBMC) instead of PEC's.

Example 317 Determination of the effect of a compound of the invention on HIV-1 LTR-driven CAT gene expression

Materials and methods

Plasmids:

p469, HIV-1 LTR driven CAT and pSV-Tat, Tat-expression vector were kindly provided from Dr. Joseph Sodroski, Dana-Farber Cancer Institute(C.A. Rosen, J.G. Sodroski and W.A. Haseltine, Cell Vol.41, 813-823, 1985, A Caputo, J.G. Sodroski and W.A. Haseltine, J. AIDS, Vol. 3, 327-379, 1990).

Medium:

RPMI 1640 medium (Life Technologies, Grand Island, NY, USA) was supplemented with heat-inactivated fetal calf serum (FBS; Sigma, St. Louis, MO, USA).

Cells:

Human T lymphoma cell line, Jurkat, was cultured in medium described above .

Transfection;

Introduction of plasmid DNA into cells was carried out according to the method described in Chiang, J. Li et. al., Proc. Natl. Acad. Sci. Vol. 92, 5461-5464

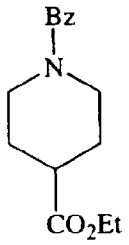
(1995). Briefly, the cells were suspended with the medium at 2 x 10^7 cells/ml followed by addition 1 mg of p469 and 0.5 mg of DEAE-dextran (Sigma). In some experiments the cells were co-transfected with 0.5 mg of pSV-Tat. After 10 minutes incubation at room temperature with occasionally mixing, the cells were pulsed with electroporation apparatus at 140 V. The cells were re-suspended with the fresh medium and cultured for 20 hours at 37°C.

Determination of the effect of a compound of the invention on HIV-1 LTR-driven CAT gene expression.

A compound tested was dissolved in dimethyl-sulfoxide at 100 mM as a stock solution. The aliquots of the stock solution were kept frozen at -20°C. Jurkat cells transfected with p469 were treated with 10 ng/ml of phorbol 12-myristate 13-acetate (PMA; Sigma) to activate HIV-1-LTR directed CAT gene transcription in the presence of the compound. In the case of cells transfected with p469 and pSV-Tat, they were simply treated with the compound. After the cells were cultured for an additional 24 hours at 37°C, the cells were washed 2 times with phosphate-buffered saline and lysed in 50 mM Tris-HCl plus 15% glycerol with repeated cycles of freeze and thaw. The cell lysates were clarified by centrifugation followed by determination of protein concentration by Bradford method (Bio-Rad, Hercules, CA, USA). Measurement of a CAT activity in cell lysates was carried

out according to a similar method described in Fridovich-Keil J. L. et. al., Cell Growth and Differentiation, Vol. 2, 67-76(1991). Equal amount (30 mg of protein) of cell lysates was incubated at 37°C with 35 mg of acetyl co-enzyme A (GIBCO/BRL, Grand Island, MO, USA) and 0.1 mCi of ^{14}C-chloramphenicol (Dupont, NEN Boston, MA, USA) in 42 ml solution for 2 hours. Acetyl-^{14}C-chloramphenicol was extracted with 9 volumes of ethyl acetate and fractionated on a TLC gel with 1:19 (v/v) in methanol/ chloroform. The CAT activity was detected by autora-diography and quantified by an Imaging Densitometer (model GS-700; Bio-Rad).

Reference Example 1 Synthesis of ethyl 1-benzoyl-isonipecotate



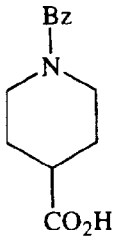
To an ice cold solution of ethyl isonipecotate (60 g, 0.382 mol) and triethylamine (38.65 g, 0.382 mol) in tetrahydrofuran (360 ml) was added dropwise benzoyl chloride (53.7 g, 0.382 mol) over a period of about 2 hours under nitrogen atmosphere. The reaction mixture was stirred for about 2 hours at the same temperature, and was filtered. The filtrate was evaporated in vacuo. The residue was partitioned between dichloromethane and

water. The organic layer was dried over magnesium sulfate, and evaporated in vacuo. Crystallization from isopropyl alcohol gave the titled compound (90.9 g).

Melting point: 71-72°C

^{1}H-NMR ($CDCl_3$): δ 1.27 (3H, t, J=7.3), 1.70 (4H, m), 2.57 (1H, m), 3.05 (2H, m), 3.75 (1H, m), 4.16 (2H, q, J=7.3), 4.54 (1H, m), 7.40 (5H, m)

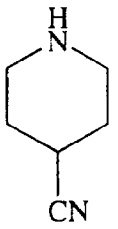
Reference Example 2 Synthesis of 1-benzoylisonipecotic acid



To an ice cold solution of isonipecotic acid (90 g, 0.697 mol) and potassium carbonate (81 g, 1.31 mol) in water (1.3 liter) was added dropwise benzoyl chloride (81 ml, 0.697 mol) over a period of about an hour at about 5°C. The mixture was stirred at room temperature overnight. The reaction mixture was acidified with 6 N hydrochloric acid and extracted with dichloromethane. The organic layer was washed with water and then dried over magnesium sulfate and the solvent was evaporated in vacuo. Crystallization from isopropyl alcohol-diethyl ether to give the titled compound (154.4 g).

Melting point: 143-144°C

Reference Example 3 Synthesis of 4-cyanopiperidine



To vigorously stirred isonipecotamide (75 g, 0.585 mol) was added dropwise phosphorus oxychloride (182 ml) over a period of about 30 minutes. The reaction mixture was refluxed for about further 2 hours, the reaction mixture was evaporated in vacuo. The residue was poured onto ice (about 600 g) to decompose an excess of phosphorus oxychloride. The aqueous solution was neutralized with sodium hydrogencarbonate and then made basic with 2 N sodium hydroxide. The aqueous layer was extracted 4 times with chloroform (500 ml each). The organic layer was dried over sodium sulfate, and evaporated in vacuo. The residue was distilled in vacuo (b.p. 70°C, 3 mmHg) to give the titled compound (50.9 g) as an oil.

Industrial Applicability

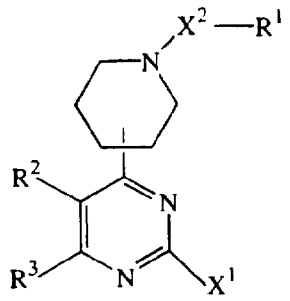
The piperidinylpyrimidine derivatives of the present invention exhibit an excellent TNFα inhibiting activity and are useful as TNFα inhibitors. The piperidinylpyrimidine derivatives of the present invention not only will normalize the abnormal TNFα production indicating immunopathy caused by viral infection but also will inhibit the proliferation of HIV.

And they also inhibited HIV-LTR transcriptional activation in vitro. Therefore, the piperidinylpyrimidine derivatives of the present invention are expected to be effective for the treatment of AIDS.

The piperidinylpyrimidine derivatives of the present invention are also expected to be useful for the treatment of diseases wherein a TNFα level reportedly is increased in blood and/or tissue, e.g., osteoarthritis, rheumatoid arthritis, multiple sclerosis, Kawasaki disease, inflammatory bowel diseases such as ulcerative colitis or Crohn's disease, Behçet disease, systemic lupus erythematosus, graft versus host disease (GvHD), multiple organ failure, malaria, meningitis, hepatitis, non-insulin-dependent diabetes mellitus, asthma, adult respiratory distress syndrome (ARDS), tuberculosis, atherosclerosis, Alzheimer's disease, etc.

CLAIMS

1. A method for inhibiting the production or secretion of tumor necrosis factor in a patient in need of such inhibition, which comprises administering to a patient a pharmaceutically effective amount of a compound represented by formula (1)



(1)

wherein X^1 is amino or hydroxyl;

X^2 is carbonyl (-(CO)-), carbonyloxy (-(CO)O-), carbonylamino (-(CO)NH-), or sulfonyl ($-(SO_2)-$);

R^1 is an alkyl, a cycloalkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_m-$ A, wherein m is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and A is a halogen atom, a cycloalkyl, hydroxy, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl,

R^2 is hydrogen, an alkyl, or an aryl;

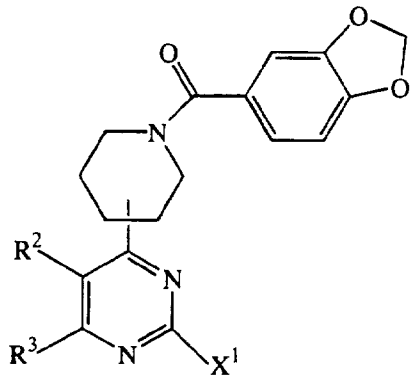
R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-$ A', wherein m' is an integer selected from

the group consisting of 1, 2, 3 and 4, and A' is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl,

or R^2 and R^3 are combined with the pyrimidine ring to form quinazoline or a pyridopyrimidine;

or a pharmaceutically acceptable salt thereof.

2. A method for inhibiting human immunodeficiency virus-1 long terminal repeat transcriptional activation in a patient in need of such inhibition, which comprises administering to a patient a pharmaceutically effective amount of a compound represented by formula (1-e)



(1-e)

wherein X^1 is amino or hydroxy;

R^2 is hydrogen, an alkyl, or an aryl;

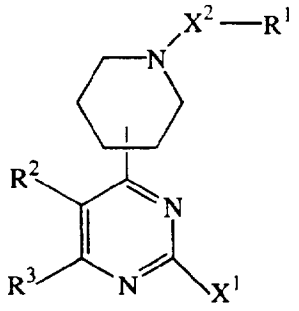
R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-$ A', wherein m' is an integer selected from the group consisting of 1, 2, 3 and 4, and A' is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro,

carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl,

or R^2 and R^3 are combined with the pyrimidine ring to form quinazoline or a pyridopyrimidine;

or a pharmaceutically acceptable salt thereof.

3. A compound represented by formula (1-a),



(1-a)

wherein

(1) X^1 is amino or hydroxyl;

X^2 is carbonyl (-(CO)-), carbonyloxy (-(CO)O-), carbonylamino (-(CO)NH-), or sulfonyl (-(SO_2)-);

R^1 is an alkyl, a cycloalkyl, an aryl, a substituted aryl, a heteroaryl, or -$(CH_2)_m$- A, wherein m is an integer selected from the group of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, and A is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkokycarbonyl, an aryloxycarbonyl, an alkyloxy-carbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl,

R^2 is hydrogen, an alkyl, or an aryl;

R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-$ A', wherein m' is an integer selected from the group consisting of 1, 2, 3, and 4, and A' is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

or

(2)X^1 is amino;

X^2 is carbonyl (-(CO)-);

R^1 is an C_{6-10} alkyl, a cycloalkyl, an aryl substituted by two or three halogen atoms, 2, 3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, a C_{7-15} aralkyl or $-(CH_2)_m-$ A, wherein m is an integer selected from the group consisting of 6, 7, 8, 9, and 10, and A is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, carboxyl, an alkoxy, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxy-carbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl or a substituted aryl;

R^2 and R^3 are combined with pyrimidine ring to form quinazoline, substituted quinazoline, pyridopyrimidine, or substituted pyridopyrimidine;

or a pharmaceutically acceptable salt thereof.

4. A compound of claim 3, wherein X^1 is amino.

5. A compound of claim 3, wherein X^1 is amino or hydroxyl;

X^2 is carbonyl (-(CO)-), carbonyloxy (-(CO)O-),

carbonylamino (-(CO)NH-), or sulfonyl (-(SO_2)-);

R^1 is an alkyl, a cycloalkyl, an aryl, a substituted aryl, a heteroaryl, or -$(CH_2)_m$- A, wherein m is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, and A is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkokycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

R^2 is hydrogen, an alkyl, or an aryl;

R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or -$(CH_2)_{m'}$- A', wherein m' is an integer selected from the group consisting of 1, 2, 3, and 4, and A' is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

or pharmaceutically acceptable salt thereof.

6. A compound of claim 3, wherein X^1 is amino;

X^2 is carbonyl (-(CO)-), carbonyloxy (-(CO)O-), or carbonylamino (-(CO)NH-);

R^1 is a cycloalkyl, an aryl, a substituted aryl, a heteroaryl, or -$(CH_2)_m$- A, wherein m is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, and A is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an

alkylthio, an alkokycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

R^2 is hydrogen, an alkyl, or an aryl;

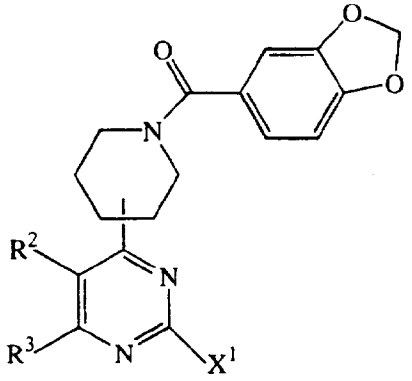
R^3 is an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-$ A', wherein m' is an integer selected from the group consisting of 1, 2, 3, and 4, and A' is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl.;

or a pharmaceutically acceptable salt thereof.

7. A compound of claim 6, wherein X^2 is carbonyl (-(CO)-), or carbonylamino (-(CO)NH-) or a pharmaceutically acceptable salt thereof.

8. A compound of claim 6, wherein X^2 is carbonyl (-(CO)-) or a pharmaceutically acceptable salt thereof.

9. A compound represented by formula (1-e)



(1-e)

wherein X^1 is amino or hydroxy;

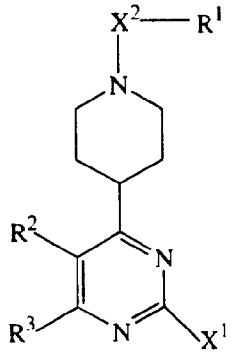
R^2 is hydrogen, an alkyl, or an aryl;

R^3 is an alkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-$ A', wherein m' is an integer selected from the group consisting of 1, 2, 3 and 4, and A' is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an alkylthio, an alkoxycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or heteroaryl;

or R^2 and R^3 are combined with the pyrimidine ring to form a quinazoline or a pyridopyrimidine;

or a pharmaceutically acceptable salt thereof.

10. A compound represented by formula (1-b)



(1-b)

wherein X^1 is amino;

X^2 is carbonyl (-(CO)-), carbonyloxy (-(CO)O-), or carbonylamino (-(CO)NH-);

R^1 is a cycloalkyl, an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_m-$ A, wherein m is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, and A is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, nitro, carboxyl, an alkoxy, an

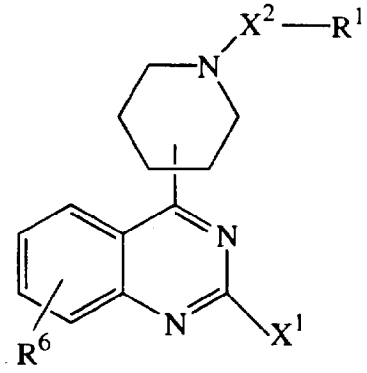
alkylthio, an alkokycarbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic, an aryl, a substituted aryl or a heteroaryl;

R^2 is hydrogen, or an alkyl;

R^3 is an aryl, a substituted aryl, a heteroaryl, or $-(CH_2)_{m'}-$ A' (wherein m' is an integer selected from the group consisting of 1 and 2, and A' is an aryl, a substituted aryl or a heteroaryl.);

or a pharmaceutically acceptable salt thereof.

11. A compound represented by formula (1-d),



(1-d)

wherein X^1 is amino;

X^2 is carbonyl (-(CO)-);

R^1 is an C_{6-10} alkyl, a cycloalkyl, an aryl substituted by two or three halogen atoms, 2, 3-methylenedioxyphenyl, 3, 4-methylenedioxyphenyl, a C_{7-15} aralkyl or $-(CH_2)_m-$ A, wherein m is an integer selected from the group of 6, 7, 8, 9, and 10, and A is a halogen atom, a cycloalkyl, hydroxyl, amino, cyano, carboxyl, an alkoxy, an alkoxy-carbonyl, an aryloxycarbonyl, an alkyloxycarbonylamino, an alkylamino, a dialkylamino, a saturated heterocyclic,

an aryl or a substituted aryl;

R^6 is a halogen atom, an alkyl, an alkoxy, nitro, cyano, carboxyl, hydroxyl, amino, trifluoromethyl, an alkylamino, a dialkylamino, an alkanoyl, an alkanoylamino, sulfamoyl, an alkylaminosulfonyl, a dialkylaminosulfonyl or an alkoxycarbonyl;

or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 97/01240

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 C07D405/14 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 101, no. 28, 1984 Columbus, Ohio, US; abstract no. 151875u, page 719; XP002034996 see abstract	1,3,11
A	& JP 05 976 082 A (KYOWA HAKKO KOGYO CO.) 28 April 1984	1,3,11

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
10 July 1997	23.07.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Francois, J